EXHIBIT 1

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC.,
PELVIC REPAIR SYSTEM
PRODUCTS LIABILITY LITIGATION

MDL No. 2327

THIS DOCUMENT RELATES TO ALL
WAVE ONE CASES INVOLVING THE PROLIFT
AND PROLIFT +M PRODUCTS

RULE 26 EXPERT REPORT OF BOB SHULL, M.D.

The following report is provided pursuant to Rule 26 of the Federal Rules of Civil Procedure. The opinions which are held and expressed are as follows:

I. QUALIFICATIONS

I am Dr. Bob Shull. My Curriculum Vitae (attached as **Exhibit A**) reflects my training, background, and publications. I graduated from Tulane Medical School and completed my residency training in Obstetrics and Gynecology at the University of Virginia in Charlottesville.

Throughout my career, I have had an interest in pelvic floor disorders of women, including pelvic organ prolapse and stress urinary incontinence. I have published original work in scientific journals regarding the evaluation and surgical management of these disorders.

Currently, I am Professor in the Division of Gynecology and member of the Section of Female Pelvic Medicine and Reconstructive Pelvic Surgery at the Scott and White Memorial Clinic and Hospital, Texas A&M System Health Science Center College of Medicine, in Temple, Texas. In this role, I maintain an active patient practice, supervise and teach medical students, residents, and fellows, and participate in clinical and basic science research. I also teach and lecture throughout the United States and in other parts of the world, often leading "hands-on" surgical workshops for colleague physicians.

I have significant experience with pelvic repair surgery of all types. I have performed many pelvic surgeries for both incontinence and/or prolapse. I have lectured nationally and internationally regarding these surgeries, outcomes, and complications. I have personally examined, diagnosed and treated approximately one hundred patients with mesh complications and removed some mesh from at least 70 women. I am familiar with the Prolift and Prolift+M kits specifically, as well as mesh products generally. I have also published articles in peer-

reviewed journals relating to complications of synthetic mesh devices for prolapse repair, including Prolift.[1]

In formulating my opinions and preparing this report, I relied on my experience, the scientific literature, and corporate documents from the files of Ethicon, Inc. ("Ethicon"). The corporate documents were supplied to me by counsel.

II. SUMMARY OF OPINIONS

The following summarize my opinions in this case:

1. At the time of its introduction, there was insufficient scientific evidence supporting the implantation of the Prolift and Prolift+M devices for pelvic organ prolapse.

2. The Prolift and Prolift+M devices (and similar prolapse mesh "kits") represented a significant departure from traditional surgical procedures performed for pelvic organ prolapse.

3. The vagina is a different environment from the abdominal wall. Maintenance of vaginal compliance and distensibility is essential for bowel, bladder, and sexual function.

4. Insertion of a mesh device containing arms and involving the blind passage of trocars presents specific risks and is inconsistent with sound pelvic reconstructive surgical principles.

5. Traditional surgical repairs are effective. The medical literature does not show improved outcomes with the use of the Prolift or Prolift+M devices or any other transvaginally placed mesh.

6. Mesh is associated with severe, life-changing complications that are not seen with traditional pelvic reconstructive surgery and are often difficult to treat.

7. Mesh removal surgery is complex and requires special expertise. Removal may not alleviate the patient's symptoms and may, in fact, make the symptoms worse.

8. The characteristics of polypropylene mesh when implanted vaginally for pelvic organ prolapse including chronic inflammation, foreign body reaction, fibrosis and scarring, nerve entrapment, deformation, stiffening, shrinkage and contraction, and degradation have clinical significance.

[1] e.g. Huffaker, Shull, and Thomas, A serious complication following placement of posterior Prolift, Int Urogynecol J (2009) 20:1383–1385; Brubaker and Shull, A perfect storm, In t Urogynecol J (2012) 23:3-4

9. Ethicon did not provide doctors and patients with complete and accurate information regarding the complications associated with the Prolift and Prolift+M devices and their management.

10. Ethicon failed to disclose the lack of benefit of pelvic organ prolapse surgery using the Prolift and Prolift+M devices to physicians and patients.

11. There are no proper clinical trials demonstrating safety of the Prolift and Prolift+M devices before their introduction into the commercial market.

12. Ethicon should have anticipated the serious and permanent complications that are caused by the Prolift and Prolift+M mesh kits.

13. From a clinical perspective, Ethicon did not exercise due diligence in the design and development of the Prolift and Prolift+M devices.

14. Ethicon lacked scientific rigor in the testing and reporting of its pelvic floor products.

15. Ethicon did not heed the warnings from the hernia and gynecologic literature regarding the use of polypropylene mesh.

16. If Ethicon had properly tested its products, certain problems and complications would have been identified before they were used in a clinical setting.

17. Ethicon inappropriately marketed the Prolift and Prolift+M products to all physicians and did not properly train these physicians in the unique aspects of patient selection and patient counseling of long-term sequelae of trocar-based meshed kits.

18. After the products were used in general clinical setting, Ethicon did not systematically monitor their products or evaluate physician feedback.

19. The problems associated with Prolift and Prolift+M devices are inherent in the concept and design and occur even when the device is placed properly.

III. THE PROLIFT PROCEDURE (AND SIMILAR MESH "KITS") REPRESENTED A SIGNIFICANT DEPARTURE FROM SURGICAL PRACTICES AT THE TIME AND YET ETHICON DID NOT EXERCISE DILIGENCE IN THE DESIGN AND DEVELOPMENT OF THE PROLIFT AND PROLIFT+M DEVICES

The Ethicon Prolift and Prolift+M devices (and other polypropylene mesh "kits" designed for the treatment of pelvic organ prolapse) represented a radical departure from surgical practices at the time of their introduction. Implantation of the Ethicon Prolift, using trocars and

arms into spaces gynecologists were not familiar with created special risks.[2] These new "systems" were very different from mesh slings used to treat stress urinary incontinence.

The Prolift Pelvic Floor Repair System is a packaged kit complete with a uniquely shaped, pre-cut synthetic polypropylene mesh, Prolift trocars/guides, Prolift cannulas, Prolift retrieval devices, and a Prolift Surgical Guide and IFU. The Prolift Pelvic Floor Repair System come in three variations – the Prolift Anterior Pelvic Floor Repair System (for the treatment of cystocele), the Prolift Posterior Pelvic Floor Repair System (for the treatment of rectocele), and the Prolift Total Pelvic Floor System (for the treatment of cystocele, rectocele, and vaginal vault prolapse). Each Prolift kit includes mesh of identical composition and manufacturing as Gynemesh PS. Ethicon marketed Gynemesh PS for use in hernia surgery. The mesh is shaped and pre-cut for use in a specific compartment of the vagina.

The Prolift+M[3] Pelvic Floor Repair System is essentially identical to the Prolift system with the exception that the mesh grafts are composed of Ethicon's Gynemesh M mesh. Gynemesh M mesh has the same composition and construction as Ethicon's UltraPro, mesh constructed of a combination of absorbable (poliglecaprone or monocryl) and nonabsorbable (polypropylene) components. Ethicon marketed UltraPro for use in hernia surgery.

At the time the Prolift and Prolift+M devices were introduced, 2005 and 2008 respectively, there was insufficient scientific evidence that supported utilization of this specific system.[4] Case reports in the literature described problems with other, similar devices. Adverse events were occurring and being reported with all types of vaginal mesh for prolapse repair. There had been complications with some synthetic slings. Surgeons were discussing complications at scientific meetings. "Mesh complications" became a frequent topic at conferences. In fact, the little literature available plus a healthy degree of skepticism should have raised serious questions about the wisdom of the use of mesh kits used for vaginal surgery. The vagina is known to be a very different environment compared to the abdominal cavity and abdominal wall – areas where mesh had been placed previously.[5] Some of the unique features of the vagina include bacterial contamination,[6] dense innervation and vascularization (controlling sensation and function), close proximity to bowel and bladder, and the need for compliance and distensibility for bowel, bladder, and sexual function.

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[2] Prior to marketing the Prolift, an Ethicon marketing executive after watching a demonstration observed that the procedure to implant a Prolift would require a "major mind shift" for surgeons. ETH.MESH.02282833.

[3] UltraPro mesh was discussed internally as early as January 2005 (prior to the Prolift going on the market) as a potentially safer alternative mesh than Gynemesh PS which was used in the Prolift. UltraPro was thought to reduce scar contraction and lower the density of the scar formation. Neither animal studies nor trials were conducted to substantiate this claim before the launch of Prolift+M. *See* ETH.MESH.01760853- ETH.MESH.01760861.

[4] ETH.MESH.01160159, Gynemesh Prolene Soft mesh, pre-clinical functionality testing strategy, 11-1-2001, Conclusion: "Based upon the Gynemesh Prolene Soft mesh's product characteristics, intended clinical indications and the use of existing polymer materials, additional pre-clinical functionality testing is not required." *See* Giselle Bonet dep., 102:1-7 ("Q. At the time the Prolift was launched, the Prolift itself had not been studied in clinical studies, correct, meaning the actual packaged product with the preformed mesh and the instruments, that had not been studied clinically, correct? A. Correct.")

[5] ETH.MESH.00164607 ("The vagina is NOT the abdomen (nor similar to any other surgical environment").

[6] P1659; P1627.

Ethicon justified the development of mesh kits based on the presumption of high recurrence rates with traditional reconstructive procedures using native tissue repair.[7]

However, the underlying assumption of high reoperation rates is not supported by the literature. Using current definitions of "success," traditional surgery has been shown to be effective (with less than 10% reoperation rate) and is not significantly improved by the use of mesh, even in the anterior compartment. According to a recent review by Stanford, most studies show an anatomic success rate around 92% for native tissue repairs – identical to mesh repairs. (Stanford, 2012). When Chmielewski reanalyzed Weber's results from her 2001 study using contemporary, clinically relevant criteria for success, she found only 11% of subjects experiencing anatomic recurrence beyond the hymen, 5% of subjects experiencing symptomatic recurrence, and no subjects requiring surgery for recurrence or complications at 1 year. (Chmielewski, 2011).

Additional studies have confirmed the success of native tissue repairs. Oversand found that 94% of 699 women with native tissue repairs of pelvic organ prolapse expressed subjective satisfaction with low reoperation rates. (Oversand, 2013). Funk et al. examined the records of 27,809 anterior prolapse surgeries from insurance records. Of these, 24.7% included mesh. The 5-year cumulative risk of any repeat surgery was significantly higher for vaginal mesh versus native tissue (15.2 % vs 9.8 %) with a 5-year risk of mesh revision/removal of 5.9%. The 5-year risk of surgery for recurrent prolapse was similar between vaginal mesh and native tissue groups (10.4 % vs 9.3 %). (Funk, 2013). Gutman and Sokol have reported a randomized controlled trial with native tissue vs. mesh-augmented anterior repairs at one and three years. (Gutman and Sokol, 2013). The authors found no objective or subjective benefit, a mesh erosion rate of >15%, and a higher reoperation rate with mesh repairs. All reoperations for recurrence were in the mesh group. The authors concluded that the rate of surgery for recurrent prolapse was no different with or without mesh. The mean time to reoperation for recurrence reported in the literature is twelve years, lending little credence to efficacy results in short term studies. (Hagen, 2006).

There are no studies showing improved surgical outcomes using mesh in the posterior or apical compartments. Furthermore, there has never been a demonstration of better anatomic or functional results in the posterior or apical compartments.

Reoperation rates for all repairs are higher with mesh due to the need for surgical management of mesh complications. Current literature suggests that mesh procedures may also promote prolapse in compartments where mesh is not placed. Withagen et al. studied this issue,

[7] ETH.MESH.03904451. Ethicon's rationale for the introducing the Prolift was predicated on the failure rate. Howeer, initial Prolift advertising in 2006 claimed "less than 5% failure rate" at 3 months following implantation. Ethicon internal documents at that time, however, showed an approximately 20% failure rate – "Prof Jacquetin's data has not proved as positive as hoped – showing approx. 80% success rate – The data will be initially presented at IUGA in September. Note that this data is a retrospective study of over 100 patients using TVM technique, not necessarily used with Prolift. This less than 90% success rate forces us to differentiate Prolift from the TVM technique moving forward." ETH.MESH.00741137. Ethicon did not inform doctors that the failure rate at 12 months was 18.4%.

finding that "[t]ension-free vaginal mesh treatment of one vaginal compartment prolapse seems to provoke the development of vaginal prolapse in initially unaffected vaginal compartments." (Withagen et al., 2010). In my experience, surgeons are seeing apical (uterus, vaginal vault, or enterocele) prolapse through the scarred distal vagina resulting from mesh repairs. The apical compartment prolapse may be exaggerated after mesh placement because the other vaginal compartments are rigidly fixed in place.

The studies demonstrating good results with traditional prolapse repairs are consistent with my experience and give an accurate representation of success rates following native tissue prolapse repairs. A new surgical innovation, whether involving a device or not, should document equivalent efficacy; equal or superior intraoperative complication rates, post-operative recurrence rates, and re-operation rates before touting their product for widespread use. In addition, there should be a description of possible complications, how to avoid them and how to manage them.

IV. THE SERIOUS AND LIFE-CHANGING COMPLICATIONS CAUSED BY THE PROLIFT AND PROLIFT+M DEVICES WERE FORESEEABLE AND NOT DISCLOSED TO PHYSICIANS AND PATIENTS

A. The Serious and Life-Changing Complications Caused by the Prolift and Prolift+M Devices Were Foreseeable

Synthetic mesh implanted in the vagina using a kit such as the Prolift and Prolift+M products can cause life-altering and sometimes permanent injury and disability. These complications were foreseeable based on the medical and scientific literature, the known properties of polypropylene, experience with other similar devices, and adverse event reporting. By 2006, there was substantial evidence in the literature describing mesh complications with erosion at a significantly higher rate. Ethicon internal documents and studies indicate that postoperative vaginal erosion/extrusion occurred in 14.1% of cases. Over 50% of these exposures required surgical treatment.[8] The scientific literature bears this out this out as well. Female pelvic surgeons, especially those of us in academic positions and referral centers, are spending a great deal of time managing mesh complications and performing challenging and risky mesh explant or removal surgeries. Ethicon knew that the Prolift and Prolift+M devices were associated with a high rate of complications. Ethicon documents supporting this opinion can be found in Section VIII.a.

There is a great deal of scientific literature dealing with the material properties of polypropylene mesh and the host response. Reported mesh characteristics include chronic inflammation and foreign body reaction,[9] bacterial contamination,[10] shrinkage and contraction,[11]

[8] ETH.MESH.00081035; ETH.MESH.00081083; ETHC.MESH.00080954; ETH.MESH.00081006; ETH-01121-01122; ETH.MESH.00081000; ETH-01322.

[9] Elmer, C., B. Blomgren, C. Falconer, A. Zhang, and D. Altman. "Histological Inflammatory Response to Transvaginal Polypropylene Mesh for Pelvic Reconstructive Surgery." J Urol 181, no. 3 (Mar 2009): 1189-95; Smith, T. M., S. C. Smith, J. O. Delancey, D. E. Fenner, M. O. Schimpf, M. H. Roh, and D. M. Morgan. "Pathologic

Continued on following page

fibrosis and scarring,[12] embrittlement,[13] nerve involvement,[14] deformation,[15] and degradation.[16] Smaller pore, heavier weight meshes, like Gynemesh PS, are thought to intensify these reactions.

Studies also characterize the properties of Gynemesh, specifically. Some examples follow. In a study by Jones, Gynemesh was the stiffest of the meshes studied. Letouzey, et al., measured the shrinkage of Gynemesh with ultrasound over a nine year period in 40 patients.

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Evaluation of Explanted Vaginal Mesh: Interdisciplinary Experience from a Referral Center." Female Pelvic Med Reconstr Surg 19, no. 4 (Jul-Aug 2013): 238-41; Iakovlev V., Carey ET, Steege J. "Pathology of Explanted Transvaginal Meshes." International Journal of Medical, Health, Pharmaceutical and Biomedical Engineering 8, no. 9 (2014).

[10] Boulanger, L., M. Boukerrou, C. Rubod, P. Collinet, A. Fruchard, R. J. Courcol, and M. Cosson. "Bacteriological Analysis of Meshes Removed for Complications after Surgical Management of Urinary Incontinence or Pelvic Organ Prolapse." Int Urogynecol J Pelvic Floor Dysfunct 19, no. 6 (Jun 2008): 827-31; Vollebregt, A., Troelstra, A., & van der Vaart, C. H. . "Bacterial Colonisation of Collagen-Coated Polypropylene Vaginal Mesh: Are Additional Intraoperative Sterility Procedures Useful?". International Urogynecology Journal and Pelvic Floor Dysfunction 20, no. 11: 1345-51.

[11] Klinge, U., Klosterhalfen, B., Muller, M., Ottinger, A. P., & Schumpelick, V. "Shrinking of Polypropylene Mesh in Vivo: An Experimental Study in Dogs." The European Journal of Surgery 164, no. 12 (1998): 965-69; Velemir, L., J. Amblard, B. Jacquetin, and B. Fatton. "Urethral Erosion after Suburethral Synthetic Slings: Risk Factors, Diagnosis, and Functional Outcome after Surgical Management." Int Urogynecol J Pelvic Floor Dysfunct 19, no. 7 (Jul 2008): 999-1006; Tunn, R., A. Picot, J. Marschke, and A. Gauruder-Burmester. "Sonomorphological Evaluation of Polypropylene Mesh Implants after Vaginal Mesh Repair in Women with Cystocele or Rectocele." Ultrasound Obstet Gynecol 29, no. 4 (Apr 2007): 449-52; Feiner, B., and C. Maher. "Vaginal Mesh Contraction: Definition, Clinical Presentation, and Management." Obstet Gynecol 115, no. 2 Pt 1 (Feb 2010): 325-30; Jacquetin, B., and M. Cosson. "Complications of Vaginal Mesh: Our Experience." Int Urogynecol J Pelvic Floor Dysfunct 20, no. 8 (Aug 2009): 893-6.

[12] Klosterhalfen, B., K. Junge, and U. Klinge. "The Lightweight and Large Porous Mesh Concept for Hernia Repair." Expert Rev Med Devices 2, no. 1 (Jan 2005): 103-17; Cobb, W. S., K. W. Kercher, and B. T. Heniford. "The Argument for Lightweight Polypropylene Mesh in Hernia Repair." Surg Innov 12, no. 1 (Mar 2005): 63-9.

[13] Junge, K., U. Klinge, A. Prescher, P. Giboni, M. Niewiera, and V. Schumpelick. "Elasticity of the Anterior Abdominal Wall and Impact for Reparation of Incisional Hernias Using Mesh Implants." Hernia 5, no. 3 (Sep 2001): 113-8; Costello, C. R., S. L. Bachman, B. J. Ramshaw, and S. A. Grant. "Materials Characterization of Explanted Polypropylene Hernia Meshes." J Biomed Mater Res B Appl Biomater 83, no. 1 (Oct 2007): 44-9.

[14] Klosterhalfen, B., K. Junge, and U. Klinge. "The Lightweight and Large Porous Mesh Concept for Hernia Repair." Expert Rev Med Devices 2, no. 1 (Jan 2005): 103-17; Bendavid, R., Lou, W., Koch, A., Iakovlev, V. "Mesh-Related Sin Syndrome. A Surreptitious Irreversible Neuralgia and Its Morphologic Background in the Etiology of Post-Herniorrhaphy Pain." International Journal of Clinical Medicine 5 (2014): 799-810; Iakovlev V., Mekel G., Blaivas J. "Pathological Findings of Transvaginal Polypropylene Slings Explanted for Late Complications: Mesh Is Not Inert [Abstract]." International Continence Society Meeting Annual Meeting (2014); Iakovlev V., Carey ET, Steege J. "Pathology of Explanted Transvaginal Meshes." International Journal of Medical, Health, Pharmaceutical and Biomedical Engineering 8, no. 9 (2014).

[15] Margulies, R. U., C. Lewicky-Gaupp, D. E. Fenner, E. J. McGuire, J. Q. Clemens, and J. O. Delancey. "Complications Requiring Reoperation Following Vaginal Mesh Kit Procedures for Prolapse." Am J Obstet Gynecol 199, no. 6 (Dec 2008): 678 e1-4.

[16] Coda, A., R. Bendavid, F. Botto-Micca, M. Bossotti, and A. Bona. "Structural Alterations of Prosthetic Meshes in Humans." Hernia 7, no. 1 (Mar 2003): 29-34; Costello, C. R., S. L. Bachman, B. J. Ramshaw, and S. A. Grant. "Materials Characterization of Explanted Polypropylene Hernia Meshes." J Biomed Mater Res B Appl Biomater 83, no. 1 (Oct 2007): 44-9.; Iakovlev, V., Guelcher, S., Bendavid, R. "In Vivo Degradation of Surgical Polypropylene Meshes: A Finding Overlooked for Decades." Virchows Arch Suppl 1 (2014): S35; Clave, A., H. Yahi, J. C. Hammou, S. Montanari, P. Gounon, and H. Clave. "Polypropylene as a Reinforcement in Pelvic Surgery Is Not Inert: Comparative Analysis of 100 Explants." Int Urogynecol J 21, no. 3 (Mar 2010): 261-70.

They found a 10% per year shrinkage rate up to 85% at 8 years.[17] Liang (2013) found that Gynemesh caused more vaginal degeneration in primate implantation than other less stiff meshes. Feola (2013) found that Gynemesh resulted in deterioration of the biomechanical properties of the vagina – more so than less stiff meshes.

New studies document the increasing rates of severe complications associated with mesh, the difficulty treating these complications, the need for multiple surgeries, the failure of corrective surgery to alleviate the symptoms in many instances, and the life-changing disabilities women suffer. New onset chronic pain syndromes following mesh implantation are the most difficult conditions to manage. Sadly, many injured women are in worse condition after mesh implantation than they were prior to having the original surgery. These particular severe complications are not seen following traditional surgeries. (Hansen, 2014; Dunn, 2014; Abbott, 2014; Unger, 2014).

I watched videos of the implantation of the Prolift Anterior, Prolift Posterior, and Prolift Total. The video demonstrates how the arms of the mesh can become string-like and are no longer flat, as they are pulled through cannulas that have been threaded through the tissue.[18] Not only during implantation but after, the Prolift and Prolift+M arms are put under a considerable amount of strain, which may ultimately lead to mesh curling, roping, and deformation.[19] This issue of deformation of the Ethicon mesh is not explained in the Ethicon literature. Ethicon knew that the trocars, cannulas and mesh arms on the Prolift and Prolift+M products would cause tissue damage during implantation as well as after implantation due to the inflammatory response of the surrounding tissue to the mesh implant. Support for this opinion can be found in Section VIII.a.

When the mesh deforms, it becomes a cord-like, rigid, and taut instrument that can saw into the tissue, causing the pain that I see frequently in these patients. This issue was not addressed prior to the introduction of the Prolift devices and has turned out to have significant clinical implications. This phenomenon was reported by Feiner and Maher in their paper, Vaginal Mesh Contraction: Definition, Clinical Presentation, and Management, published in 2010. The authors concluded that vaginal mesh contraction is "a serious complication after prolapse repair with armed polypropylene mesh that is associated with substantial morbidity, frequently requiring surgical intervention." (Feiner and Maher, 2010).

Letouzy, et al. reviewed the long-term changes in pelvic mesh volumes over time using three-dimensional translabial ultrasonography and found mean contraction of 30%, 65%, 85% at follow-up durations of 3, 6, and 8 years, respectively. This study demonstrates that the

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[17] Letouzey V., et al. "Ultrasound evaluation of polypropylene mesh contraction at long term after vaginal surgery for cystocele repair." Int Urogyn J 2009;20(Suppl.2):S205-6.

[18] ETH.MESH.00419571-00419600 (Prolift Systems Surgical Technique guide).

[19] ETH.MESH.00034875, email 11-20-2008 from Jonathan Meek to Catherine Lepley and others: "Another point is that the tight-knit arms would result in a rope effect. Knowing that the tissue needs to grow through the arms as-well, this will be problematic in the patient. To be fair, it is an issue for everyone because if you 'yank' Gynemesh arms, they will also lose their porosity. The effect of roping is increased inflammatory response, increased risk of infection and denser scar plate (not much fun for the patient) …"; ETH-80647.; Kirkemo dep. (4-18), at p.135-138, p.150; Hinoul dep. (4-6), p.506-507.

pathological process that causes mesh shrinkage is progressive and there is linear evolution of the contraction rate with time, raising the concerning possibility that mesh contraction continues indefinitely.

At the IUGA Conference in 2009, the inventor of the transvaginal mesh technique used in the Prolift system, Professor Jacquetin, presented data indicating that painful mesh contraction occurred at a rate of 19.6%.[20]

From my review of Ethicon documents, I find no evidence that there was a systematic evaluation of the introduction of the actual cannulas, trocars, and retrieval devices in the female pelvis, grasping the arms of the mesh, and pulling the trocar and then the cannula back through multiple tissue layers in a highly vascularized and innervated area prior to the Prolift System being placed on the market. Ethicon apparently utilized the trocars and cannulas on cadavers.[21,22,23,24] However, cadavers are not a substitute for *in vitro*, *in vivo* studies or the mesh or careful investigation laboratory, animal and human trials. It is well known that cadaveric tissue does not maintain the same properties that are present in the tissue of a living human being. The main benefit of the cadaver model is to demonstrate gross anatomical landmarks, but a hemi-pelvis from a cadaver does not help the surgeon to understand individual anatomical variations. A cadaver cannot be used to evaluate the tissue response, nerve or blood vessel damage, anatomic or functional outcomes, safety concerns, or in vivo characteristics of the product. Support for these opinions can be found in Section VIII.a.

The serious complications associated with transvaginally placed mesh kits are now well-known to surgeons practicing in the area of female pelvic reconstructive surgery, and well-described in the medical literature. If Ethicon had performed the indicated testing before clinical marketing proceeded, including bench testing, animal studies, clinical trials, and examination of explanted meshes, these problems would have been identified.

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[20] L. Velemir, B. Fatton, B. Jacquetin: mesh shrinkage: How to asses, how to prevent, how to manage. IUGA Como, Italy, June 16-20, 2009.

[21] ETH.MESH . 02277482.

[22] The first Prolift Clinical Expert Report, dated November 10, 2004, reads as follows: "Cadaveric evaluations of prototype PROLIFT components have demonstrated that these devices and the system as a whole are suitable for use in performing pelvic floor repairs. These evaluations, in conjunction with all other elements required by Ethicon PR563-001, support release of a total of 30 kits to experienced D'Art clinical investigators in order to obtain an in-vivo assessment of system performance. This assessment is intended as an adjunct of Design Validation activities to confirm that evaluations made in cadaveric specimensreflect actual use." ETH-41142.

[23] 2-7-2005, ETH-01624, Prolift Design Validation, Comment: "Participant indicated that the ability for the cannula to facilitate user access to the retrieval device is poor." [Ethicon] response: "… during deep passages the tip of the cannula tended to get lost in deep tissues." In this context, "lost" means that the surgeon has to move the cannula around in the "deep tissue" of critical structures, including organs, arteries, veins, and nerves, while trying to retrieve the device. Damage caused by this maneuvering would not be evident in a cadaver.

[24] 2-7-2005, ETH-01626, Prolift Design Validation, Comment: "Entrance points were well defined but the exit points are not so clear." If the exit points of the cannula-equipped guides cannot be reproduced consistently, this increases the risk of damage to organs and major neurovascular structures in the pelvis and increases the risk of procedure failure if mesh is not secured correctly in the relevant supporting structures.

B. Ethicon knew about complications associated with their products and did not inform doctors as to how to manage them

I have reviewed the Ethicon Instructions for Use (IFU) and patient and doctor brochures for these products. Reviewing the information contained in these documents is something I do on a regular basis in my practice and in my capacity as an educator of medical students, residents, and colleague physicians. In my opinion, these documents do not provide adequate information for doctors and patients to make informed choices. They do not include the severity and frequency of the complications, a complete list of potential complications, the lack of clinical data to support their use, the difficulty in removing mesh, and the occurrence of permanent disability. The product literature also does not provide information regarding contraindications to the use of the product in women with fibromyalgia, painful bladder syndrome, or other chronic pain conditions. Ethicon documents supporting this opinion can be found in Section VIII.b.

The most obvious complication missing from the adverse reaction list is chronic pain. Severe and intractable pain following mesh prolapse repair is the most serious problem I see regularly in patients referred to me for the treatment of mesh complications. Ethicon knew that chronic pain could be a significant postoperative problem when these products are utilized in vaginal surgery, and yet it is not mentioned in Prolift 510(k) applications, labeling (IFU), or physician and patient education materials. Even though postoperative pain can occur with traditional prolapse surgery (vaginal prolapse repair with native tissue utilizing sutures or abdominal sacrocolpopexy), debilitating, life-altering pain following these procedures has rarely been a significant issue. When post-operative pain occurs, it is usually temporary, treatable, and typically does not result in long-term disability. Pain as a result of trocar placed, armed mesh kits is often life-altering and can be permanent. Ethicon was aware of this lack of viable treatment options, and should have investigated and recognized the complication of new onset and progressive pelvic pain and determined if effective treatment options were available or if this complication was preventable prior to marketing a permanently implanted medical device.

Ureter obstruction was identified by Ethicon in August 2007 as comprising 20% of post-operative complications over a 5-month period in 2007. It was raised as a serious issue because of the rapid progression into hydronephrosis and compromised renal function within a short period of time. Despite an indication of concern regarding the rate and potential severity of this complication, as well as acknowledgement that physicians did not seem certain how to address this complication when confirmed, the Prolift IFU implemented in December 2007 did not include any indication of urinary obstruction or retention, or ureteral obstruction in its warnings or adverse reaction listings. In 2005, voiding dysfunction was also identified as a post-operative problem which did not resolve for a year in some patients. It was not until 2009 that the Prolift IFU listed urinary retention/obstruction, ureteral obstruction, and voiding dysfunction as adverse reactions.

Another serious problem involves the removal of transvaginally placed mesh when complications do arise. Corrective surgeries for mesh complications are often lengthy, risky (due to the potential for further damage to nerves, bladder and bowel, and further scarring and retraction), invasive, and frequently do not completely resolve the problem. When urogynecolgists started seeing these severe complications, there were no established treatment

guidelines. Many specialists now have a significant portion of their practices occupied with handling mesh complications. Ethicon should have considered how to avoid or if unable to avoid how to manage the complications that they knew would occur and developed protocols for their management. Ethicon should also have communicated these protocols to the physicians they were training to implant their Prolift devices.

The Prolift IFUs stated throughout the time the product was on the market that: "The mesh remains soft and pliable, and normal wound healing is not noticeably impaired. The material is no absorbed, *nor it is subject to degradation* or weakening by the action of the tissue enzymes."[25] Ethicon failed to inform physicians and patients accurately and completely through the labeling and marketing materials. This information would have been important to physicians in evaluating the risks and benefits of the Prolift device which was intended to be a permanent implant for the life of the patient. This information would also have been important for physicians to know in order that they might have a complete informed consent discussion with their patients.

In its own materials, Ethicon described the Prolift Pelvic Floor Repair System as utilizing a "revolutionary" surgical technique. Ethicon should have considered how to avoid, recognize, and manage the complications that they knew would occur and developed protocols for their management. Ethicon should also have addressed these complications and communicated the protocols to the physicians they were training to implant their Prolift devices.[26, 27] Ethicon received requests from physicians regarding such additional instruction, but no company documents were found supporting a change in training protocols.[28] The blind insertion of the trocars through the obturator foramen, ischiorectal fossa, ileococcygeus muscle and sacrospinous ligament is a drastic departure from traditional non-mesh surgery, which is performed under direct vision. Ethicon was aware of the degree of discomfort physicians had with the procedure from feedback during training courses, as well as the high percentage of surgeons who needed to be retrained.[29,30] This percentage was surprisingly high, considering Ethicon was initially very selective as to the skill level those attending training sessions.[31]

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[25] ETH.MESH .02341526 (emphasis added). The IFU maintained this claim throughout the time the Prolift was on the market.

[26] ETH.MESH.00847816 (Comment from Dr. Butrick to Ethicon Medical Director, David Robinson: "I sure am tired of seeing these pts with bad myofascial pain after Prolifts. The doctors need to be taught how to identify pf pain disorders and avoid placing meshes thru these spastic muscles.")

[27] ETH.MESH.02289896 (slide from Dr. Butrick, "The aggressive surgery flares the pre-existing myofascial pain…"

[28] ETH.MESH.01184009 (2009 Surgeon Summit Breakout Session – February 7 Survey Results: "The improvements requested for PROLIFT are mostly around training; this is felt to be a big need. There is not sufficient education regarding peri-obturator anatomy and there is a failure of surgeons to understand the anterior apical passage."

[29] ETH.MESH.02282833 ("The consensus is that some doctors will need more than one exposure to TVM surgery before they feel confident to be able to start the procedure (even those with high skill sets)."

[30] ETH.MESH.00031359 "16 of the 84 have needed to be re-trained (19%)…"

[31] ETH-83128

Other well-known complications Ethicon failed to cite in their warnings include nerve damage (sometimes permanent), vaginal scarring,[32] de novo stress urinary incontinence, other bladder and bowel dysfunction, impairment of sexual function, foreign body reaction to synthetic products, chronic infection, recurrence of prolapse, and partner discomfort or injury with sexual intercourse.

At the time the Prolift was marketed and sold, Ethicon was aware of issues with erosion, infection, scarification, and the significant problems these issues could create.[33] However, I could not find any Ethicon documents advising surgeons how to treat these complications. The warning label should have stated that polypropylene lasts a lifetime and complications may require additional surgeries that may or may not correct the newly acquired problems. Doctors should have been told that these complications were serious and could be life altering for their patients.

C. Ethicon did not inform doctors as to which patients were poor candidates for the Prolift procedure

The IFUs for the Prolift Products include the following contraindication: "When GYNECARE GYNEMESH PS mesh is used in infants, children, pregnant women, or women planning future pregnancies, the surgeon should be aware that this product will not stretch significantly as the patient grows."[34] There is nothing to document specifically who would most likely benefit from the product use. Patient selection is important. Ethicon should have determined and informed doctors what subpopulations of women were appropriate candidates for their products or more importantly, who is not a satisfactory candidate.

When a device or operation does not have a proven track record, this information can only be obtained through clinical trials. One example is the use of these prolapse mesh kits in women who have a pre-existing history of chronic pelvic pain. It is my opinion that mesh products should not be used in women with a history of chronic pelvic pain.

Another example where extreme caution should have been used is in women who are sexually active. It is my opinion that the risk of dyspareunia is unacceptably high following the placement of a prolapse mesh kits and that they should not be used in women who are sexually active unless the patient is extensively counseled on the possibility that her sexual function will be significantly and permanently impaired.

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[32] ETH.MESH.03021946 ("Pelvic Floor materials are still over-engineered . . . we need less foreign body material . . we need: Materials that correlate to measured female pelvic physiological characteristics."

[33] P.1659.

[34] ETH.MESH.02341522; ETH.MESH.02341454. In 2009, Ethicon added contraindications: "GYNECARE GYNEMESH'" PS Mesh must always be separated from the abdominal cavity by peritoneum. GYNECARE GYNEMESH'" PS Mesh must not be used following planned intra-operative or accidental opening of the gastrointestinal tract. Use in these cases may result in contamination of the mesh, which may lead to infection that may require removal of the mesh. The GYNECARE PROLIFT' System should not be used In the presence of active or latent infections or cancers of the vagina, cervix, or uterus." ETH.MESH.02341734.

Studies after commercialization of the Prolift suggest that patients who have diabetes and women who smoke have a much great risk of erosion. Ethicon should have provided this information to physicians so that they could properly counsel their patients.

D. Ethicon formed a special interest group with other mesh manufacturers to further market its prolapse mesh kits

Ethicon (along with American Medical Systems, Bard, and Boston Scientific Corporation) gathered a group of mesh proponents to form the Pelvic Health Coalition to influence reimbursement. Publicly, the PHC claimed to be "committed to raising awareness of pelvic prolapse by promoting and expanding patient, public, and professional education; promoting advocacy efforts; and strengthening the voice of the pelvic prolapse community" However, internal documents reveal that the organization had one primary mission – "the purpose being to improve hospital reimbursement for pelvic floor procedures which utilize synthetic or autologous products".[35]

The PHC petitioned the Centers for Medicare and Medicaid Services to create additional codes and "add-in" codes for mesh grafts for prolapse repair procedures. The PHC claimed that these codes would allow for "better data collection, outcomes research, and enhance the - quality of women's health care."[36] Ethicon rationalized the increased reimbursement based on shorter operating times (not proven), lower reoperation rates (not proven). Ethicon, under the guise of the PHC also attempted to postpone the FDA's public health notification[37] and claimed credit for the change in language of the ACOG Practice Bulletin #79.[38]

V. THERE ARE SAFER ALTERNATIVES TO THE USE OF THE PROLIFT AND PROLIFT+M POP MESH KITS THAT ARE EFFECTIVE AND HAVE VIRTUALLY NONE OF THE DEVASTATING COMPLICATIONS SEEN WITH THESE PRODUCTS

There are safer alternatives to the Prolift mesh devices. As discussed previously, the whole premise of transvaginal mesh kits was based on the inaccurate perception of high recurrence rates when traditional reconstructive procedures using native tissue repair were performed. However, the underlying assumption of high rates of recurrence is not supported by the literature. Devastating complications could have been predicted and did, in fact, occur. These severe complications had virtually never been reported with traditional native tissue repairs. Unlike mesh repairs including the Prolift procedure, the complications of native tissue repairs are known and the treatments are well-established.

[35] ETH.MESH.00136420, ETH.MESH.00738769, ETH.MESH.01280816, ETH.MESH.01280860, ETH.MESH.00720002.
[36] ETH.MESH.00720002.
[37] ETH.MESH.02312098.
[38] ETH.MESH.02316434.

For surgical treatment of cystocele, an anterior colporrhaphy or site-specific native tissue repair using suture is quite effective with success rates of about 90%. Complications are infrequent, treatable, and related to the surgery itself and the immediate post-operative period. Of course, mesh erosion does not occur. Other complications, such as chronic pain or debilitating dyspareunia are uncommon.

A rectocele is traditionally treated with posterior colporrhaphy, a procedure to plicate the subepithelial vaginal connective tissue. Painful intercourse can occur following a posterior repair, but is uncommon as a long-term problem.

Surgical options for women with vaginal apical prolapse include transvaginal suspension procedures using native tissue and sutures, such as sacrospinous ligament fixation and uteroscaral ligament suspension or sacral colpopexy, which can be performed abdominally, laparoscopically, or robotically. Although sacral colpopexy uses synthetic mesh, it does not have the same risks of new onset pelvic pain or the same likelihood of erosion as mesh placed vaginally.

In 2000, I published our experience at Scott and White with apical prolapse treated with transvaginal reconstructive surgery with native tissue. In this series of 302 patients, 87% had optimal anatomic outcomes, with no persistent or recurrent support defects at any site. Thirteen percent had one or more sites with at least grade 1 loss of support, but the majority of these were grade I defects detectable only on careful pelvic exam. Morbidity included a 1% transfusion rate, a 1% ureteral injury or ureteral kinking rate, and a 0.3% postoperative death rate (an 85 year old woman with dementia died at home 4 days after the surgery with no autopsy). None of the ureteral injuries resulted in permanent disability. (15). We also reported on the recognition and management of nerve entrapment pain after uterosacral ligament suspension. Eight (1.6%) of 515 patients had neuropathic pain postoperatively that was treated immediately by removing the sutures on the affected side. In all patients, the pain resolved. (16). This situation is very different from the nerve injuries and complex neuropathic pain conditions that I see with mesh. With mesh-related neuromuscular pain, the location is variable, the pain can present immediately or remotely, and the new onset pain can be very difficult to treat, often requiring more than one operation and with less than optimal success.

Paraiso et al. (1996) reported on 243 patients (mean follow-up 73.6 months) who underwent sacrospinous ligament suspension and pelvic reconstruction. Recurrence of prolapse occurred over time, but only 4.5% underwent subsequent pelvic reconstruction. Defect-free survival rates at 1, 5, and 10 years were 88.3%, 79,7, and 51.9%, respectively. I had the opportunity to review this manuscript and write the Comment. I noted the importance of the following principles needed for successful reconstructive surgery: 1) correction of all anatomic defects; 2) maintenance or restoration of normal bowel and bladder function; and 3) maintenance of the vaginal canal for sexual function. Attempting to use a standardized operation with mesh kits when an individualized approach is required invites problems after surgery. Operations for prolapse require diagnostic acumen and technical execution of a procedure that is tailored to the individual patient's anatomy, symptoms, and desires.

I reviewed the full-length articles available for the Prolift and Prolift+M Systems. I have not summarized each of them but below present my observations regarding a sample of the major studies. The published literature does not support a conclusion that the benefits of surgical repair with the Prolift or Prolift+M Systems exceed the risks. The failure rate is shown to be comparable or worse than traditional repairs. The risk of complications such as mesh exposure, mesh shrinkage/contraction, pain, dyspareunia and voiding dysfunction is unacceptably high.

A. Prolift

1. Jacquetin (2010)

This study by some of the inventors of the Prolift presented 3-year follow-up on 85 of the 90 women (94%) enrolled in the French TVM study. Of the 90 women enrolled, 14 women (16.3%) had stage II prolapse with the remaining women having stage III prolapse. The authors reported failure (recurrent prolapse > stage I) in 15 of 86 women (17.4%) at 1-year follow-up, including 1 woman with reoperation for recurrent prolapse. The authors then reported failure in 17 of 85 women (20%) at 3-year follow-up, including 3 women with reoperation for recurrent prolapse. The authors reported in this article that 12 of 90 patients (13.3%) required reoperation, 3 for recurrent prolapse, 8 for mesh exposure, and 1 with vesicovaginal fistula. Within the text of the article, 4 other patients (for a total of 16 of 90, 17.8%) were described who required reoperation, including 1 patient each with urinary retention requiring mesh release, evacuation of hematoma, hematoma leading to mesh extrusion requiring mesh resection, and mesh retraction requiring resection. Furthermore, these data did not include 14 additional patients (for a total of 30 of 90, 33.3%) who required reoperation within the first year of follow-up, including 9 patients treated with TVT-O for new stress incontinence, 1 patient with section of TVT-O for voiding impairment, 1 patient with section of vaginal adhesions, and 3 patients requiring other operations. Therefore, the authors underreported the frequency of reoperation by a factor of 2.5 times. At 1-year, moderate or severe vaginal stiffness (loss of elasticity) could be detected by digital exam in 12.6% of patients (11 of 90). No new cases were reported at the 3-year follow-up exam. Of the 61 patients who were sexually active at baseline, only 36 (59%) remained so at 3 years. The authors conclude that "Medium-term results demonstrate that the TVM technique provides a durable prolapse repair." However, the results make clear that the risks outweigh the benefits in light of the 20% failure rate, reoperation rate of 33.3%, and the fact 41% of women suffered loss of sexual activity.

2. Velemir (2011)

This study by the French TVM group assessed 91 women at least 1 year after the Prolift procedure, which included 75 anterior and 62 posterior Prolift mesh implants. Mesh retraction was estimated by palpation relative to the original length of the mesh and was defined qualitatively as absent, moderate (< 50%), or severe (≥ 50%). In addition, ultrasonography was performed to measure mesh length and thickness. Anterior mesh retraction was moderate in 80% and severe in 9.3% of patients. Posterior mesh retraction was moderate in 48.4% and severe in 9.7% of patients. With both anterior and posterior Prolift mesh implants, mesh retraction was strongly associated with increased mesh thickness and higher frequency of recurrent prolapse. In the 7 patients with severe anterior mesh retraction, maximum mesh thickness was 4.1 ± 0.9 mm,

and 5 of the 7 patients (71%) had recurrent anterior vaginal prolapse. In the 6 patients with severe posterior mesh retraction, maximum mesh thickness was 4.6 ± 1.3 mm, and 3 of the 6 patients (50%) had recurrent posterior vaginal prolapse. The authors described and depicted that severe mesh retraction resulted in lack of mesh covering the distal (closer to the vaginal opening) bladder and rectum, leading to recurrent prolapse. The authors felt this explained why the frequency of recurrent prolapse increased between 3 months and at least 1 year after the Prolift procedure, due to ongoing mesh retraction caused by the chronic inflammatory and foreign body reaction. The authors also stated that mesh retraction was probably a factor contributing to postoperative pain and dyspareunia, although clinical correlation with pain was not reported in this study. Ethicon marketed the Prolift procedure as "new" and "revolutionary" without the least understanding of how the Prolift mesh implant would behave in the vaginal environment. Ethicon knew that mesh retraction caused serious clinical consequences in hernia repair, and Ethicon had to know that those serious clinical consequences would occur at the same level, if not worse, in vaginal prolapse repair. From the first reports of the TVM technique using Gynemesh PS mesh, mesh retraction was known to be a frequent and serious complication, yet it was not included in the Prolift IFU. Ethicon failed to warn surgeons and patients of the severe clinical consequences and lack of effective prevention or treatment of mesh retraction.

3. Miller (2011)

This study, authored by Ethicon consultants and an Ethicon employee, reported the 5-year results for 66 of 85 patients (78%) originally enrolled in the US TVM study. A total of 15 of 66 patients (22.7%) met criteria for failure in the treated compartment, including 10 patients with ≥ stage II prolapse and 5 patients requiring reoperation for recurrent prolapse. Overall failure occurred in 33.3% (90% CI, 23.8-44.1%). Although the authors claimed that these results demonstrate stability of the anatomic outcomes, in fact, the TVM failure rate nearly tripled from 1 year (12%) to 5 years (33.3%).

The authors reported data inaccurately to underrepresent the true frequency of complications by using the total study population of 85 women as the denominator in reporting the frequency of complications, rather than the appropriate denominator of 66 women who attended 5-year follow-up. For example, mesh exposure was reported as 19% (16 of 85 patients), rather than the true frequency at 5 years of 24% (16 of 66 patients). Voiding dysfunction was misreported as 9% (8 of 85 patients), rather than the true frequency at 5 years of 12% (8 of 66 patients). The original Prolift IFU had no warning regarding voiding dysfunction, and the revised Prolift IFU revised only stated that normal voiding could be impaired "for a variable length of time," and did not indicate that voiding dysfunction could be prolonged, if not permanent.

Although the authors claimed that the most important finding of their study was "… the lack of new morbidity after the early (1 year) postoperative period," it would be more accurate to state that the same type of morbidity occurred again and again over the 5-year period. As reported in this article, a total of 29 of 66 women (44%) required reoperation, including 13 for stress incontinence, at least 9 for mesh exposure, 5 for recurrent prolapse, and 2 for fistulas, although the authors did not state this finding directly. The frequency of reoperation for complications was exceedingly high and vastly higher than anything reported with traditional vaginal prolapse surgery or even abdominal prolapse surgery.

Consistent with the 3-year results of the French TVM study, nearly one-third of preoperatively sexually active women abandoned sexual activity after the Prolift procedure, which strongly suggests that the TVM procedure impaired sexual activity in ways that were not assessed. However, the authors did not present the data in such a way that it was obvious that nearly one-third of the women (13 of 40, 32.5%) stopped being sexually active, and they did not discuss this in the article. Instead, by stating that only 1 woman developed new dyspareunia after the TVM procedure, the authors had the audacity to claim that their results "seem to confirm a net positive effect on sexual activity following prolapse surgery despite the use of mesh."

The authors concluded that "Five-year results indicated that TVM provided a stable anatomic repair." This is not true. However, as with the conclusions drawn from the 3-year results of the French TVM study, they provide no summary statement to indicate the human cost of achieving this so-called "stable anatomic prolapse repair," including reoperation in nearly half of the patients and loss of sexual activity in one-third of the patients. Indeed, the reoperation rate after the TVM procedure increased markedly over time, from 23-25.3% at 1 year, 33.3% at 3 years, and at least 44% at 5 years. Given the life-long risk of mesh-related complications and the deterioration of "benefit" as prolapse recurs over time, the risks of the TVM procedure greatly outweigh the benefits.

4. DeLandsheere (2012)

This study reported the results of a retrospective study after the index procedure was performed between January 2005 and January 2009, with follow-up of a median of 38 months (range, 15-63 months) in 524 women after Prolift procedures, including 48 women (9%) after anterior Prolift, 103 women (20%) after posterior Prolift, and 373 women (71%) after total Prolift procedures. In 286 women, anterior and posterior Prolift procedures were performed with uterine conservation. Of a total of 600 women in the consecutive series, 68 women were lost to follow-up, and 8 women died (including 1 woman who died of endometrial cancer 3 years after Prolift with uterine conservation). Of the 76 women not included in the primary analyses, 7 women (9.2%) had post-Prolift surgery. In the study population, 98 of 524 women (18.7%) had previous surgery for prolapse; therefore, the majority of women were having primary repair of prolapse.

Overall, 76 of 524 patients (14.5%) required reoperation after the Prolift procedure (see Table 2), although the article reported that only 61 of 524 patients (11.6%) required reoperation. A total of 19 women had reoperation for mesh complications, including 13 women with mesh exposure (within a median of 13 months from the index Prolift procedure), 1 woman with infected mesh (who subsequently developed recurrent prolapse after complete mesh excision), 2 women with mesh retraction, 2 women with rectal compression, and 2 women with vaginal synechia. One of these women had both mesh retraction and mesh exposure. In addition, 16 women had reoperation for recurrent prolapse within a median of 23 months from the index Prolift procedure. Although this article reports a lower frequency of reoperation than other articles, it must be emphasized that this represents the work of the TVM group that has the longest experience in performing transvaginal mesh prolapse surgery. Unfortunately, the other reports in the literature (including some of the early reports from the TVM group itself) demonstrate that these favorable results were not consistently reproduced in other studies.

5. The Iglesia Series (Iglesia (2010) & Sokol (2012)

Iglesia, et al. published 2 articles on the same study population with varying lengths of follow-up. The first article reported minimum 3-month follow-up and median follow-up of 9.7 months (range, .24-26.7 months); and the second reported minimum 1-year follow-up and mean follow-up of 14.7 months. The original study population consisted of 65 women with multi-compartment prolapse, 33 randomly assigned to the vaginal surgery group (most commonly treated with uterosacral ligament suspension, anterior and/or posterior colporrhaphy) and 32 women to the Prolift group (treated with anterior, posterior, or total Prolift). The data safety and monitoring board halted enrollment in the study when the mesh erosion rate surpassed the predetermined stopping criteria. Previous surgery for prolapse had been performed in only 4 of 65 women (6%); baseline prolapse was stage II in 11 of 65 patients (17%).

Recurrent prolapse as an anatomic outcome was defined as ≥ ICS POPQ stage II. By the definition of anatomic outcome, recurrent prolapse was no different in the non-mesh group compared to the Prolift group. In the non-mesh group, recurrent prolapse occurred in 70.4% at early follow-up and 69.7% at later follow-up. In the Prolift group, recurrent prolapse occurred in 59.4% at early follow-up and 62.5% at later follow-up. However, no patients in the non-mesh group required reoperation for prolapse, and 3 of 32 patients (9%) in the Prolift group had reoperation for recurrent prolapse. At each point of follow-up, no difference in symptom resolution existed between the 2 groups. The study assessed quality of life and symptoms using validated questionnaires and found no difference between the 2 groups. There was no difference in the proportion of patients with subjective cure of vaginal bulge symptoms between the non-mesh group (90%) and the Prolift group (96.2%).

Complications occurred more commonly in the Prolift group, including mesh exposure in 5 patients (15.6%). At later follow-up, 5 patients in the Prolift group required 6 operations, compared with none in the non-mesh group. Ethicon did not update the Prolift IFU to adequately inform physicians about the expected frequency of Prolift mesh erosion,

6. Altman (2011)

Altman, et al. published a randomized clinical trial comparing anterior colporrhaphy in 189 patients to the anterior Prolift procedure in 200 patients with 1-year follow-up. The primary outcome was defined as a composite of prolapse at ICS stage 0 or I and no symptoms of vaginal bulging. At 1 year, 60.8% of the Prolift group met the criteria for success, compared with 34.5% of the anterior colporrhaphy group. The Prolift group also had better results when the primary outcome was evaluated separately by its 2 components, prolapse stage and symptom of vaginal bulging. For prolapse at ICS stage 0 or I, 82.3% of the Prolift group versus 47.5% of the anterior colporrhaphy group met this criterion. For no symptom of vaginal bulging, 75.4% of the Prolift group versus 62.1% of the anterior colporrhaphy group met this criterion.

The Prolift group experienced more intraoperative and postoperative complications, including a higher frequency of reoperation after only 1 year. Reoperation was necessary in 13 patients (6.5%) in the Prolift group versus 1 patient (0.5%) in the anterior colporrhaphy group.

Average operative time was almost twice as long in the Prolift group (52.6 minutes) compared to the anterior colporrhaphy group (33.5 minutes). New stress incontinence was twice as likely in the Prolift group (12.3%) as in the anterior colporrhaphy group (6.2%). Pain with sexual intercourse was almost 4 times higher in the Prolift group (7.3%) compared to the anterior colporrhaphy group (2%). Pain was experienced more frequently in the Prolift group (inguinal pain in hospital, 2.5%; severe pelvic pain at 2 months, 2.5%; and severe pelvic pain at 1 year in 0.5%) versus in the anterior colporrhaphy group (no inguinal pain in hospital, severe pelvic pain at 2 months, 0.5%; and no severe pelvic pain at 1 year).

The majority (84%) of patients in the study population were undergoing primary repair of prolapse. About half (52%) had an early stage of prolapse (stage II, within 1 cm of the hymen); indeed, only 84% of patients experienced the symptom of vaginal bulging before surgery. ACOG/AUGS and the SGS do not recommend surgical intervention in patients who are at an early stage of prolapse and have some experienced symptoms of vaginal bulging and discomfort.

The authors cautioned that "Patients should understand, however, that the use of mesh may cause complications even after the immediate postoperative period." The authors concluded that "When one is counseling patients regarding surgical options, the benefits of the mesh kit must be balanced against the higher rates of surgical complications and postoperative adverse events associated with this approach." Because Ethicon failed to provided adequate information regarding the true risks of pain, contracture, chronic inflammation, and other adverse events to physicians through the Prolift System IFU and other materials, physicians would not have had sufficient information to properly counsel patients prior to implantation.

7. The Withagen Series

The Withagen group published 2 articles on the same study population, one with the primary 1-year outcomes of the RCT and a secondary analysis of new prolapse in the untreated compartment. In addition, a prospective cohort study reported predictors of failure after Prolift procedures. The study population was restricted to women with recurrent prolapse, although almost half (47%) had only stage II prolapse. Patients were randomly assigned to conventional prolapse repair (n=97) or Prolift procedures (n=93). Conventional prolapse repair included anterior and/or posterior colporrhaphy and sacrospinous or uterosacral ligament suspension. The Prolift procedures included anterior, posterior, or total procedures; 7 patients in the Prolift group also underwent conventional apical repair.

At 1 year, failure (defined as ≥ stage II prolapse) occurred in 38 of 84 (45%) of the non-mesh group and in 8 of 83 (9.6%) of the Prolift group. In contrast to the anatomic outcomes, subjective improvement occurred in equal proportions in both groups, 64 of 80 (80%) in the non-mesh group and 63 of 78 (81%) in the Prolift group. Both groups experienced a similar decrease in symptoms and improvement of quality of life measured by the Urogenital Distress Inventory (UDI).

Intraoperative and postoperative complications were more frequent in the Prolift group versus the non-mesh group, including bladder injury in 2 versus 0 patients, hematoma in 6 versus 1 patients, and temporary urinary retention in 16 versus 5 patients. Levels of new-onset pain,

dyspareunia, and stress incontinence were similar in both groups. In the Prolift group, 14 of 83 women (16.9%) developed mesh exposure, and 5 women required surgical treatment; 7 women had persistent mesh exposure at 1-year follow-up. In the Discussion, the authors expressed concern about the unknown effects of long-term presence of nonabsorbable mesh in the vagina and, because of this concern, suggested that Prolift be reserved for patients with recurrent prolapse.

The second article (Withagen BJOG 2012) reported a much higher frequency of new prolapse in untreated compartments in the Prolift group. At 1 year after surgery, 10 of 59 women (17%) in the non-mesh group versus 29 of 62 women (47%) in the Prolift group were diagnosed with new prolapse stage II or higher in the untreated compartment. In the Prolift group, women with new prolapse were significantly bothered as reflected in a higher score (13.1 ± 24.2) in the prolapse domain of the UDI, compared to women without new prolapse (2.9 ± 13.9). Of interest, when additional apical support was performed with anterior Prolift, the development of new prolapse was significantly reduced, underscoring the inadequacy of the anterior Prolift procedure to provide sufficient apical support.

The third article (Milani 2012) reported on 433 patients with 1-year follow-up after Prolift procedures. Failure (defined as recurrent prolapse ≥ stage II) in the treated compartment occurred in 15%. Overall failure in any compartment occurred in 41%. Failure defined as prolapse beyond the hymen and the presence of vaginal bulge symptoms or repeat surgery occurred in 9%. A consistent predictor of failure for all definitions was the combined anterior/posterior Prolift procedure with uterine conservation.

8. Maher (2011)

This article reported 2-year outcomes after laparoscopic sacral colpopexy (n=53) versus total Prolift (n=55) for women with posthysterectomy vaginal vault prolapse. Although preoperative prolapse stage was not provided, entry criterion required that women had at least stage II vaginal vault prolapse, and average baseline POPQ point C was 2.6-2.8 cm beyond the hymen, indicating advanced prolapse. Objective success, defined as < stage II prolapse at all sites, was more frequent after laparoscopic sacral colpopexy, 41 of 53 (77%), than after Prolift, 23 of 55 (43%). Symptomatic prolapse occurred in 1 woman after laparoscopic sacral colpopexy and 4 women after Prolift. Although both groups experienced similar improvements in quality of life, satisfaction was higher in the laparoscopic sacral colpopexy group (87 ± 21) than in the Prolift group (79 ± 20). The authors attributed this difference in patient satisfaction to the much higher reoperation rate in the Prolift group. In the laparoscopic sacral colpopexy group, 3 women (5.7%) had surgery (1 each for TVT, trocar hernia, and mesh erosion), and in the Prolift group, 12 women (22%) had 15 reoperations (4 for mesh contracture, 3 for suburethral tapes, 3 for recurrent prolapse, and 2 for mesh erosion). Vaginal mesh erosion occurred in 1 patient in the laparoscopic sacral colpopexy group and 7 patients in the Prolift group.

This is the only RCT comparing the Prolift with a laparoscopic sacral colpopexy. Although the laparoscopic sacral colpopexy group had longer operating time compared with the Prolift group (median 97 minutes versus 50 minutes), intraoperative blood loss was less (median

100 mL versus 150 mL), hospital stay was shorter (median 2 days versus 3 days), and patients returned to normal activity an average of 5 days sooner.

9. Frankman (2013)

This study was done to determine frequency, rate, and risk factors associated with mesh exposure in women who underwent Prolift repair. The retrospective chart review was performed for 201 women who were implanted between September 2005 and September 2008. Mesh exposure occurred in 12% (24/201), and the frequency was found to be higher when mesh was placed in the anterior compartment versus the posterior (8.7% vs. 2.9%, P=0.04). Of additional interest, the authors observed a 7-fold increased risk of mesh exposure in women with diabetes.

10. McDermott (2013)

The aim of this study was the comparison of postoperative anatomical outcomes following sacral colpopexy (SC) with outcomes following transvaginal mesh colpopexy (TVMC) with total Prolift in obese women. Fifty-six women underwent SC and 35 underwent TVMC, with a follow-up between 6 and 12 months. Follow up ranged from 6 to 12 months. SC patients showed significantly higher anterior and apical POP-Q measurements ($p<0.05$), as well as showing significant difference in overall POP-Q stage, with more recurrences in the TVMC group (32% vs. 12% in the SC group; P=0.03). The odds ratio indicated those in the obese TVMC group were 4.4 times more likely to have a stage II recurrence than those in the obese SC group.

11. Rogowski (2013)

A study done by Rogowski, et al., aimed to determine correlations between mesh retraction after anterior vaginal mesh repair and vaginal pain, de novo SUI, and overactive bladder. Subjects consisted of 103 women with stage 3 and 4 symptomatic prolapse of the anterior vaginal wall that underwent Prolift anterior implantation. Patients were interviewed at a 6-month follow-up, and underwent a cough stress test, and an introital/transvaginal ultrasound to measure the mesh length. The overall reduction in mesh length was found to be about 50% at 6-month follow-up. Mesh retraction was significantly larger (5.3 cm vs. 4.2 cm; $p<0.01$) in a subgroup of patients who reported postoperative vaginal pain (n=23; 22.3%) as compared with those that did not report pain. Additionally, a significant correlation was found ($R=0.4$, $p=0.01$) between mesh retraction and the severity of vaginal pain. Also, the percentage of patients with postoperative vaginal pain was significantly higher in the high mesh retraction group (35%) than in the low mesh retraction group (10%; $p<0.05$). Retraction was larger (5.0 cm vs. 4.3 cm; $p<0.05$) in a subgroup of patients that presented de novo OAB symptoms (n=20; 19.4%) as compared to those that did not. The percentage of these patients with de novo OAB was significantly higher in the high mesh retraction group (27%) than in the low mesh retraction group (12%; $p<0.05$). This study shows that patients with a larger amount of retraction were significantly more likely to present with both de novo OAB symptoms and de novo vaginal pain.

The authors suggest that local inflammation, neurogenic factors (e.g., nerve trapping), and /or displacement of the bladder neck may be contributory factors.

12. Khan (2014)

In order to evaluate the anatomical, functional and post-operative outcomes of Prolift, 106 subjects with either grade 2 prolapse or higher or recurrent prolapse, underwent Prolift mesh repair with anterior, posterior or total Prolift. Three (2.8%) of patients were re-operated due to recurrent prolapse in the operated compartment, and 14 (13.2%) underwent another operation due to prolapse in the non-operated compartment. At a median of 4 years, the patients were contacted and 82 agreed to a clinical review, while 19 chose a telephonic follow-up. Of the 82, 6 (7.3%) had developed a recurrence of prolapse in the operated compartment, while 16 (19.5%) had developed a prolapse in the non-operated compartment, with a total recurrence rate at 4 years of 26.8%. Upon vaginal exam, 13 (15.8%) were tender, and 3 (3.6%) had asymptomatic mesh exposure. Mesh exposure over the entire study period was noted in 6 (5.6%) women, and partial mesh excision was performed in 5. De novo SUI was found at a rate of 5.6%. Thirty-four of the 82 women were still sexually active, and 9 (26.4%) of these complained of some degree of dyspareunia. Authors considered their success rate to be 89.9%, as they did not count prolapse in another compartment as a failure because that compartment had not been treated by a Prolift mesh.

13. Kozal (2014)

Midterm morbitity and functional outcomes were assessed retrospectively with a mean follow-up of 9.5 months in 112 patients who underwent the Prolift procedure (anterior, posterior, and total). The median follow-up was 49.5 months (range: 16-85). A total of 25 subjects (22%) had postoperative and late complications, with the most common being defecation disorders (10.7%). Failure rates were found to be 8% (n=9). Surgical management was necessary for 5 patients (4.5%) who had mesh exposure. Of the 64 patients who were sexually active prior to surgery, 16.1% reported a decline due to de novo dyspareunia. De novo prolapse was seen in 13 patients (11.6%) in an initially non-treated compartment. Additionally, authors state that their results confirm the existence of a learning curve, with a significant difference in a surgeon with more than 10 surgeries.

14. dos Reis Brandao da Silveira (2015)

Authors aimed to compare the outcomes of native vaginal tissue repair with synthetic (Prolift) mesh repair in this multicenter randomized trial, which included 184 women with POP-Q stage 3 or 4. Repairs were anterior and/or posterior, and all patients with uterine prolapse received a hysterectomy. Follow-up consisted of clinic visits at 7, 30, 180, and 360 days. Ninety women were in the native tissue group, and 94 were in the mesh group. At one year, the only difference between the groups was related to mesh exposure, which occurred in 20% of patients in the mesh group, with a reoperation rate of 16.7%. The overall rate of reoperation in the native repair group was 3.7% (3 patients with recurrence), and 7.9% in the mesh group (2 patients with recurrence, 3 with exposure, 1 with wound dehiscence, and 1 with extrusion into the rectum).

Prolapse recurrence was observed in 16 patients from the native tissue group, and 7 from the mesh repair group.

15. Zhang (2015)

Investigators aimed to evaluate the incidence and predisposing factors of postoperative voiding difficulty and mesh-related complications in 206 women with stage III to IV POP who underwent a total Prolift repair in a prospective observational cohort study. The women underwent physical examination in the clinic at 3 months and every 12 months post-surgery. One hundred ninety-two women were enrolled in final data analysis and a mean follow-up period of 4.2 years (range 1 to 6 years). Bladder scan showed 60 of 192 (31.3%) of the women exhibited postoperative voiding difficulty (residual urine volume ≥ 100 mL or more than one third of voided volume), and 40 of 192 (20.8%) exhibited a residual urine volume of 200 mL or more. Twenty-nine of 192 (15.1%) reported mesh-related complications, and in most cases, women had more than one complaint. Mesh exposure and/or contraction were the most commonly reported (69%; 20 of 29). Of these, 80% (16 of 20) occurred more than 1 year after surgery. Dyspareunia was reported by 10% (2 of 20). There were 13 cases of mesh exposure that were repeated exposure which required excision. Authors suggest that women who had greater blood loss during the surgery or previous pelvic operations were prone to vaginal complications, and suggest this may be due to the presence of an increased number of scars caused by previous operations and the possibility of scar and hematoma formation impairing integration between the mesh and tissues. The authors also noted that blood loss and hysterectomy were strongly correlated. Four patients required sling surgery for SUI, all from the mesh group.

B. Prolift+M

1. Ignjatovic (2011)

This article reported the 1-year outcomes of a prospective study involving 32 patients who were implanted with Prolift+M anterior. At 1 year, POP was corrected (postoperative POP grade ≤1, the most distal point 1 cm above the level of the hymen) in 28 of 32 (87.5%) patients. Grade 0 was present in 23 of 32 (71.8%) and grade 1 in 5 of 32 (6.7%) of patients. Mesh erosion was reported in 9.3% of patients. Twenty-two patients (68.7%, mean age 53.6 years) were sexually active before the surgery and 21 (65.6%, mean age 53.2 years) after the surgery. The authors noted that postoperative sexual life could not be evaluated reliably because it was absent in a certain number of patients at the beginning of the study.

2. Milani (2011)

Milani, et al, published a prospective observational study involving 127 patients, 41 anterior, 16 posterior, and 70 total. The primary outcome was defined as anatomic success in the treated compartment at 1 year being a POP-Q stage I, without further surgical re-intervention. Anatomical success in the treated compartment was 77.4%. Of those patients without prolapse in the other compartment, 20.5% had de novo stage II prolapse develop in the untreated

compartment by 1 year. There was a statistically significant improvement in sexual function score in patients at both 3 months and 1 year post implant. At 1 year, 3.9% of patients reported pelvic pain. Thirteen patients or 10.2% had mesh exposure or erosion during year 1 with 7 undergoing mesh excision and 6 treated with topical estrogen.

3. Khandwala (2013)

This is a prospective study done in 157 consecutive subjects who were treated with the Prolift+M System, 104 total, 5 anterior, and 48 posterior, from April 2009 to November 2010. The subjects were followed at 6 weeks, 6 months, and 12 months postoperatively. 117 of the study participants had concomitant procedures, the treatment of stress urinary incontinence with TVT-O. Success was defined as a POP-Q score lower than Stage II and responses to questionnaires indicating that the patient did not have bothersome bulge symptoms and a feeling that they were "much better" post-implant. When assessed by preoperative POP-Q stage of prolapse, the composite scores were as follows: stage II, 85.3%; stage III, 88.9%; and stage IV, 89.5%. When assessed by the type of the Prolift+M mesh procedure, the breakup of the composite success scores were as follows: total, 88.6%; posterior, 86.4%; and anterior, 100%. If the lost-to follow-up subjects are considered failures, then the composite score would be 75.2% and the anatomic cure would be 80.3%. Three (2.2%) of 134 subjects had mesh exposure in the vagina. One subject underwent excision in the operating room, and 2 subjects were managed expectantly. De novo dyspareunia was noted in 3 (6%) of 50 subjects, only 37.3% of patients were sexually active preoperatively. De novo SUI was reported by 11 subjects (8.2%), and 15 subjects (11.2%) reported de novo urge urinary incontinence.

These studies raise red flags and, by no means, confirm the safety and efficacy of the Prolift and Prolift+M products.

VI. ETHICON DID NOT PERFORM PROPER CLINICAL TRIALS TO DEMONSTRATE THE SAFETY AND EFFICACY OF ITS DEVICES

From my review of the materials referenced, I was impressed by the clear absence of any systematic approach on the part of Ethicon with regard to the clinical testing of the products prior to placing the products on the market. Scott Jones acknowledged that one option available to Ethicon was to not make the Prolift commercially available until clinical trials could be conducted to establish that the Prolift product and procedure was safe and effective, but Ethicon chose to go directly to market:

> Q. Certainly one of the options to Ethicon would have been to not sell the Prolift® on a widespread commercial basis as it was and instead just limit it to experimental clinical trials until there could be solid confidence throughout the medical community that this was a safe and effective procedure and product. That was an option that Ethicon had. Correct?

A. I suppose it's always an option with any product or any company.

…

Q. Ethicon had the option to not make the Prolift® commercially available unless and until carefully controlled long-term clinical trials could prove it to be safe and effective enough to justify whatever risks there were, but rather, Ethicon chose not to do that, instead just sell it commercially as it did. Correct?

A. Ethicon did choose to commercially sell the product, if that's what the question is.[39]

The Prolift was not adequately studied before it was launched.

A critical analysis of these devices and how they would function inside a woman's body was never made before the devices were placed on the market. There were no proper randomized controlled trials with institutional review board (IRB) approval performed in the United States or abroad prior to selling these products.[40] Ethicon was aware of the lack of clinical data and the implications of not having this data. Support for this opinion is contained in Section VIII.c.

At the same time, Ethicon ignored significant evidence in the literature and their own experience with hernia mesh and Gynemesh PS mesh that would have led any reasonable person to expect the product to cause significant complications and risks.

The clinical studies Ethicon used to support the sale of the Prolift Systems are referred to as the French and US TVM studies and described above. These studies did not utilized the same mesh shapes,[41] instruments, or exact surgical procedures as the Prolift Systems. The TVM studies did not establish the safety and effectiveness of the Prolift Systems. The French TVM study failed its primary endpoint of 20% or less recurrence rate with only 1 year of follow-up, and the US TVM study met the endpoint by four-tenths of a percentage point only after Ethicon violated the original study protocol and changed the statistical parameters that defined failure versus success, in order to be able to falsely claim that at least one of the TVM studies was a success.

Overlaying these inadequacies was the complete lack of any long-term studies establishing the safety and effectiveness of the Prolift Systems. In an article accepted for publication on

[39] Jones dep., 727:19-728:4; 728:25-729:10.

[40] ETH.MESH.01160159, Gynemesh Prolene Soft mesh, pre-clinical functionality testing strategy, 11-1-2001, Conclusion: "Based upon the Gynemesh Prolene Soft mesh's product characteristics, intended clinical indications and the use of existing polymer materials, additional pre-clinical functionality testing is not required."

[41] This study, an open-label observational cohort without a control group, enrolled 90 patients from 8 sites in France and reported 12-month follow-up on 87 patients. Gynemesh PS mesh was provided by Ethicon and cut by the surgeons using a template into a shape resembling but not identical to that of the Prolift mesh implant. Although the surgeons were expected to cut the implant to the provided template, it later became evident that not all surgeons were adhering to this requirement and instead were hand-cutting the mesh implant without following the template. ETH.MESH.00401457 (Email 1-31-2006 about protocol violations, from Allie Smith: "On the French study some material was hand cut …").

September 14, 2006, and published thereafter in the International Urogynecology Journal, the French TVM Group recounted numerous complications, and concluded that long-term data were needed to establish the safety and effectiveness of the Prolift Systems – this 18 months after the Prolift Systems were first marketed.[42] Long-term studies establishing the long-term safety and effectiveness of the Prolift Systems were never conducted. Importantly, long-term studies that describe the safety and effectiveness of the Prolift Systems compared with traditional vaginal prolapse surgery were never performed.

If the Prolift System was to be used at all, it should only have been used in the context of a rigorous experimental clinical trial, under strict guidelines, with a limited and carefully selected patient population, and only with an extensive informed consent process designed to clearly notify participants that the use of the Prolift System was purely experimental, that the safety and effectiveness could not be reliably stated (hence, the need for clinical study), and that significant, life-altering complications could result, which could be untreatable.

Ethicon failed to establish a data registry for the Prolift that would have enabled it to track the results in real practice. Physicians providing feedback confirmed that data registries are more "reflective of real world experience," because: "Clinical studies use Tier 1 docs [doctors], real world experience is heavily weighted with the outcomes produced by Tier 2 and 3 doctors. Data registries more reflect the real world in the eye of many of those docs."[43] A registry would have been a very useful tool to track the outcomes of patients who underwent the Prolift procedure and permanent Prolift mesh implantation.

Ethicon resisted a proposal to start a Prolift registry in Australia, confirming in a July 13, 2006 email that this was rejected for commercial reasons. "Consequently, if none of our competitors are keeping registries, our complication data may appear increasingly accurate but with decreasing appeal…"[415]

As a physician, I expect companies to provide me with complete and accurate information. This cannot be accomplished without sufficient clinical data.

In order to evaluate these products in any meaningful way, the entire device and procedure should have been used in testing. Issues such as graft tension, maintenance of graft orientation, shrinkage tendencies, deformation of the mesh (folding, bending, bunching, and cording), potential nerve and blood vessel injuries, histologic indicators of immune and inflammatory reactions, and impact on sexual function, bladder, and bowel function should have been studied prior to introduction. Outcomes, complications, and the best ways of managing complications should have been resolved prior to marketing.

Documents supportive of this opinion can be found in Section VIII.c.

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[42] ETH-02358-02367, Fatton BF, Amblard JA, Dabadie CD, Debodinance PD, Cosson MC, Jacquetin BJ. Preliminary results of the Prolift technique in the treatment of pelvic organ prolapse by vaginal approach: a multicentric retrospective series of 110 patients. Int Urogynecol J 2006; 17: s357-360.
[43] ETH-49659.

VII. THE MEDICAL LITERATURE DOES NOT SUPPORT THE USE OF MESH KITS FOR THE SURGICAL TREATMENT OF PELVIC ORGAN PROLAPSE.

Synthetic mesh implanted in the vagina with a trocar-based, armed mesh kit such as the Ethicon Prolift products causes life-altering and sometimes permanent injury and disability without proven benefit. The literature now bears this out. Urogynecologists, especially those of us in academic positions and referral centers, spend a great deal of our time managing mesh complications and performing challenging and risky mesh removal surgeries.

I have reviewed the reliable scientific literature regarding the use of transvaginal mesh for prolapse repair. From these studies (and confirmed by my clinical experience), I have made the following conclusions regarding the efficacy of these products:

1. There is no good evidence supporting improved benefit in quality of life (QOL) or relief of symptoms *in any compartment* with the use of transvaginal mesh for the treatment of pelvic organ prolapse.
2. There is no reduction in reoperation rates for prolapse *in any compartment* with the use of transvaginal mesh for the treatment of pelvic organ prolapse.
3. There is no evidence of anatomic benefit with the use of transvaginal mesh for the treatment of pelvic organ prolapse in the posterior or apical compartments.
4. Initially it appeared as if there might be some *anatomic* benefit in the anterior compartment. These findings are now reliably disputed and any anatomic benefit obtained is frequently a result of scarring and at the expense of proper function.
5. The total number of reoperations is higher in mesh repairs due to the rate of surgeries for repair of complications.

I have made the following conclusions regarding the safety of these products from my review of the scientific literature:

1. Adverse events and complications are common.
2. Many of these complications do not occur with traditional prolapse repairs.
3. Many of these complications are life-altering and permanent, unlike those seen with traditional prolapse repairs.
4. Many of these complications require additional surgery which may *or may not* alleviate the symptoms - unlike traditional prolapse repairs.
5. Sometimes, multiple surgeries are required.
6. These complications can occur at any time – months or years after the original surgery, unlike complications occurring with traditional prolapse repairs.
7. Explant surgery, when indicated, is risky, difficult to perform, and may or may not alleviate symptoms.

I have concluded the following regarding the differences regarding the mesh complications and those associated with traditional surgery:

1. Many of the complications reported occur only with mesh. These include erosion and extrusion, mesh contraction syndrome, organ perforation from mesh, partner injury,

severe vaginal pain, granulomas, and need for multiple surgical procedures for removal and attempted relief of pain.

2. Mesh complications, as opposed to complications with traditional repairs, are likely to be more frequent and more severe. Examples include dyspareunia, de novo stress urinary incontinence, chronic pelvic pain, neuromuscular injury, and emotional sequelae.
3. Most mesh complications are more difficult to treat. This includes fistulae, bleeding, infection, bowel/bladder injuries, dyspareunia, pelvic pain, and recurrent prolapse.
4. The potential for complications lasts indefinitely because the synthetic mesh is permanent and virtually impossible to remove in its entirety.
5. Some risks are still unknown and cannot be known for many years to come.

These opinions are based on a broad familiarity with the medical literature. The FDA reached many of these same conclusions in its white paper on the use of transvaginal mesh dated July 2011. Additional publications have appeared in the literature since the time of its publication, offering further support for these opinions. (e.g. Abbott, 2014; Lee, 2014). In short, the risks of armed, trocar-based prolapse mesh kits (such as the Prolift and Prolift+M products) far outweigh any benefits.

VIII. EXAMPLES OF ETHICON DOCUMENTS SUPPORTING THESE OPINIONS

The following sections give examples of Ethicon documents I have reviewed which support my opinions, but the supportive documents are not limited to those that are shown below.

a. Complications Caused by the Prolift Devices Were Foreseeable

ETH.MESH.01220730: (2/10/2004)

- Erosion is still a primary concern because it is the symptom or result of the scar formation around and on the mesh. The identification of the collagen fibrils' orientation and eventual contraction will be the measurement of how well we are succeeding in reducing the scar formation. The two are both important and I would use one to identify the potential for the other in this early stage work.

- What are the other materials/construct ideas being considered by Gynecare as second generation products to Gynemesh PS?

Redacted

- Additionally, I am open to other alternate material suggestions.

Contraction of Scar Tissue

- Has contraction of scar tissue been reported with use of Gynemesh PS?
- Yes it has. However, the only way it is specifically identified is when the repair fails and the surgeon needs to re-operate. Otherwise the complications which could indicate scar contraction, such as pain or tension (i.e.pulling or pressure) in normal circumstances can not be directly identified as due to the contraction, because every thing is internal and can not be seen. Also, female sexual dysfunction due to pain can be attributed to an over tightening of the vaginal tissue or scar adhesions between the vagina and rectum or bladder.

ETH.MESH.00584846

From: Kammerer, Gene [ETHUS]
Sent: Mon, 10 May 2004 16:20:27 GMT
To: Melican, Mora [ETHUS] <MMELICAN@ETHUS.JNJ.COM>; Brown, Kelly [ETHUS] <KBrown8@ETHUS.JNJ.com>; Gosiewska, Anna [ETHUS] <AGosiews@ETHUS.JNJ.com>
CC: Walji, Zenobia [ETHUS] <ZWalji2@ETHUS.JNJ.com>
Subject: FW: Mesh for TVM

Here is some input from the Gynecare European unit regarding mesh used for pelvic floor repair. Pro. Jacquetin is the inventor of the Pelvic floor repair technique Gynecare will be marketing next year. We are working very closely with him and Dr. Cosson to develop it. Based on this information and other communications I have had it seems our competition is ahead of us in this area. We need to think about how we can fast forward this project, get more support from both Gynecare and Ethicon as well as quickly optimize the construction. Kelly, let's add this in to our meeting agenda tomorrow.

Gene
-----Original Message-----
From: Berthier, Ophelie [JNJFR]
Sent: Monday, May 10, 2004 11:39 AM
To: Walji, Zenobia [ETHUS]
Cc: Bonet, Giselle [ETHUS]; Kammerer, Gene [ETHUS]; Arnaud, Axel [JNJFR]
Subject: Mesh for TVM

Zenobia,

I know you are working on new mesh materials with Gene and I'd like to share with you the inputs of Pr Jacquetin and Dr Cosson.

Their main concern is now the shrinkage of the mesh which may lead to pain, dyspareunia...Indeed now that they have tremendously improved the technique and lowered the erosion rate what needs to be improved is the shrinkage of the mesh (in this case gynemesh soft).

ETH.MESH.00681364

From: Walji, Zenobia [ETHUS]
Sent: Tue, 07 Sep 2004 13:50:29 GMT
To: Bonet, Giselle [ETHUS] <GBonet3@its.jnj.com>; Bell, Steve [ETHIT] <SBell6@ethit.JNJ.com>
CC: Mahar, Kevin [ETHUS] <KMahar@its.jnj.com>; Breznak, Mike [ETHUS] <MBREZNAK@ETHUS.JNJ.com>
Subject: FW: Pelvic Floor Monthly - August Report - Next Gen Materials Progress

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Dear Giselle (and Steve),

(SENSITIVE AND CONFIDENTIAL INFORMATION - Please do not share with anyone without discussing with me first)
Ronnie, Gene and I have had several meetings with CBAT (Center for Biomaterials and Advanced Technology group) to review their lab learnings from investigating several composite materials and therefore provide some direction for a Next Gen Pelvic Floor Material:

A) GYNEMESH PS + Bovine Collagen/Gag Matrix (Integra = Advanced Wound Care product used for Burns patients)
B) GYNEMESH PS + Proceed (Interceed + PDS - FYI this is a composite mesh released by EPD)
C) GYNEMESH PS + Europa (35% PCL, 65% PGA = CBAT material)

The key insights related to orientation of the collagen fibrils and therefore characteristics that could positively improve/reduce tissue contraction around the mesh. GYNEMESH PS today has a "swirling effect" causing what doctors have expressed as "shrinkage or contraction of the mesh". It isn't the mesh that's contracting, its the tissue that seems to be "bunching" up resulting in the desire to have a more "tension-free" fixation.
Bottom line, if you have collagen trails in ONE Direction, it is likely to cause MORE contraction.
Therefore, collagen trails that are multidirectional/more random may be BETTER to reduce contraction.

ETH.MESH.00442831:

-----Original Message-----
From: Kammerer, Gene [ETHUS]
Sent: Tuesday, January 18, 2005 11:21 AM
To: Brown, Kelly [ETHUS]
Cc: Yang, Chunlin [ETUS]; Walji, Zenobia [ETHUS]; Engel, Dr. Dieter [ETHDE]; Holste, Dr. Joerg [ETHDE]; Parisi, Paul [ETHUS]
Subject: RE: Proposal for work with CBAT

Kelly,
Are we beginning to make the samples? If so, I think we were going to do the synthetic material first then the collagen. If help is needed, I am available.

On another note, I spoke with Prof Mauro Cervigni today. He is an Italian gynecologist. He uses Gynemesh and Pelvicol to do a tension free pelvic floor repair. We talked about his requirements for an ideal mesh, what problems he is having with his current materials, and a lot about his procedure and technique. Some important points which he made:
1) infection is present in 8% of his cases and leads to erosions, therefore an antibiotic action in the mesh is needed. Erosion is present in 10% to 8% of his cases. He always sees an low grade fever associated with erosion, whether or not the infection actually is detected.
2) faster tissue repair would prevent complications of erosion and Dyspareunia, the later generally caused by scar contraction
a. contraction pulls against the side wall and causes pain
b. it causes a hard tissue which can be felt by patient and sexual partner
c. it can lead to a balling up of the mesh which is very uncomfortable
d. it can lead to suture line dehiscence
e. it can lead to prolapse recurrence

ETH-18761 (January 18, 2005):

Thank you also for your notes on the conversation with Prof. Mauro Cervigni. I find the perceived correlations between infection, mesh acceptance/tissue healing and vascularity intriguing (particularly in light of our proposed test samples that may aid vascularity). I also find the comments about mechanical property needs to be useful. I would like to learn more about UltraPro Mesh - perhaps we can include it in our battery of samples at some stage. In general, I am always pleased to learn of the commonalities in surgeons' observations. Many of the points that Prof. Cervigni mentioned have been voiced by other surgeons which gives me a degree of confidence in considering these issues in our innovative efforts.

Kelly

ETH.MESH.04945233

-----Ursprüngliche Nachricht-----
Von: Kammerer, Gene [ETHUS]
Gesendet: Mittwoch, 13. April 2005 18:27
An: Barbolt, Thomas [ETHUS]; Holste, Dr. Joerg [ETHDE]; Dormier, Edward [ETHUS]; Batke, Boris [ETHDE]
Cc: Angelini, Laura [ETHIT]; Guidry, Cyrus [ETHUS]; Schwartz, Barbara [ETHUS]; Engel, Dr. Dieter [ETHDE]; Storch, Mark L. [ETHUS]; Savidge, Sandy [ETHUS]; Brown, Kelly [ETHUS]
Betreff: RE: ULTRAPRO vs PROLENE Soft Mesh
Vertraulichkeit: Vertraulich

Tom,
Regarding which attributes to investigate to show a difference between materials, I have this input. The issue which I am trying to investigate/solve is one of scar contracture around the mesh. In pelvic floor repair even with the PSM, we have seen some scar contracture which translates into procedural complications. I don't want to state % here because the situation which produces the complication is in itself complicated and specific to each patient. Also, most of the data comes from VOC and not our documented studies. However, it is important to know that the surgeons who are our consultants on the ProLift product are asking for a mesh which is better than PSM in this area.
The complications which are identified in the market are 1) recurrence of the prolapse 2) pain 3) stiffness 4) erosion and 5) discomfort during sex. The surgeons attribute these conditions to scar contracture. If we could find a way to reduce the scar formation by some % and subsequently the contracture it would give us a significant advantage over the competition as well as make the procedure better for the patient. One way to prove this is, as you stated, by identifying the tissue reaction attributes which are directly associated with scar formation and contracture. Start with in vitro studies and then in vivo studies to show a specific link and a clear

b. Ethicon Knew about Complications and Did Not Inform Doctors How to Manage Them

P1704.

Prolift®: experience of the University hospital of Clermont-Ferrand

Prospective study	**Prolift®: patients operated on between March 2005 and August 2006**
Follow-up	18 months [12-27]
Patients included -available for follow-up	125 patients 107 patients
Mean age	66.7 years [42-87]
Menopause - HRT	118 patients (94.4%) 29 patients (23.2%)
Previous POP surgery	37 patients (29.6%)
Previous hysterectomy	45 patients (36%)
Previous SUI surgery	23 patients (18.4%)
Surgical procedure	**Anterior Prolift: 32.8%** **Posterior Prolift: 16%%** **Total or Ant+Post Prolift: 51.2% (20.1% + 31.2%)**
Mesh exposure rate - 3 months - max f/u	**11.2%** **14%**
Painful mesh shrinkage	**19.6%**
Global objective success rate	**75.7%** **POPQ<2 (-1cm)**

P.1704, p.23

Functional results : painful mesh shrinkage

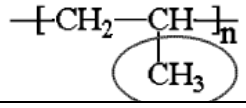
- Painful mesh shrinkage (at vaginal examination)
  - 21 patients (19.6%)
    - 13 sexually active
      - 5 without dyspareunia
      - 2 dyspareunie “often” (VAS 5 and 8 respectively)
      - 3 dyspreunia “sometimes” (VAS 5)
      - 3 didn’t complete the questionnaire
    - 8 sexually inactive
      - 1 became sexually inactive because of dyspareunia

Correlation between painful mesh shrinkage and dyspareunia but not systematic

ETH.MESH.02589066

Polypropylene can suffer from degradation following implant

- Polypropylene has a long history of use but it is subject to degradation; a process which initiates after a few days post implantation in animal studies[1]
  - This study proposes oxidation as the degradation mechanism, reporting that polypropylene filaments containing an antioxidant were less susceptible to oxidation
  - Oxidation usually occurs at the tertiary repeating position in the polymer, where a free radical is formed that then reacts with oxygen, followed by chain scission to produce aldehydes and carboxylic acids. In external applications, it shows up as a network of fine cracks that become deeper and more severe with time of exposure
  - Degradation of polypropylene has also been reported in the eye, where sutures were used to implant an intraocular lens[2] ; the authors suggest enzymatic degradation
  - Macrophages excrete acidic compounds that can initiate oxidation processes[4]
  - One clinician interviewed proposed that variability in the raw materials, and/or processing thereof, could be affecting the clinical performance and outcomes. He articulated his intention to investigate this hypothesis
  - High resolution images[3] of excised meshes clearly show physical degradation of polypropylene filaments



ETH.MESH.00031359

From: Vie, Amy [ETHUS]
Sent: Wed, 18 May 2005 00:16:20 GMT
To: Munchel, Kendra [ETHUS] <KMunchel@ETHUS.JNJ.com>; London Brown, Allison [ETHUS] <ALondon@ETHUS.JNJ.com>; Mahar, Kevin [ETHUS] <KMahar@ETHUS.JNJ.com>; Zipfel, Robert [ETHUS] <RZipfel@ETHUS.JNJ.com>; Campbell, Lori [ETHUS] <LCampbe3@ETHUS.JNJ.com>; Jones, Scott [ETHUS] <SJones34@ETHUS.JNJ.com>; Vasquez, Domingo [ETHUS] <DVASQUE1@ETHUS.JNJ.com>; Parisi, Paul [ETHUS] <PParisi@ETHUS.JNJ.com>; Kaminski, Marianne [ETHUS] <MKaminsk@ETHUS.JNJ.com>; Prine, Greg [ETHUS] <GPrine2@ETHUS.JNJ.com>
CC: Lane, Erika [ETHUS] <ELane@ETHUS.JNJ.com>; Chilcoat, Susie [ETHUS] <SChilco2@ETHUS.JNJ.com>; De Lacroix, Bruno [ETHUS] <BDelacr2@ETHUS.JNJ.com>; Castillo, Jeffrey [ETHUS] <JCastil9@ETHUS.JNJ.com>; Lech, Tom [ETHUS] <TLech@ETHUS.JNJ.com>
Subject: Summary of Prolift Training YTD

16 of the 84 have needed to be re-trained (19%), and all of these surgeons were first trained via cadaver labs. To my knowledge, we have not had a surgeon attend a preceptorship and request cadaver training.

ETH.MESH.00757011 [Note: Dyspareunia was not included in the 12/14/2007 IFU, it first appeared in 2009]

From: COSSON Michel <M-COSSON@CHRU-LILLE.FR>
Sent: Thu, 02 Feb 2006 09:39:34 GMT
To: Ciarrocca, Scott [ETHUS] <SCiarro2@its.jnj.com>; Bernard Jacquetin (E-mail) <bjacquetin@chu-clermontferrand.fr>; COSSON Michel <M-COSSON@CHRU-LILLE.FR>
CC: Robinson, David [ETHUS] <DRobin11@its.jnj.com>; Berthier, Ophelie [EESFR] <oberthie@its.jnj.com>; Bonet, Giselle [ETHUS] <GBonet3@its.jnj.com>
Subject: RE : PROLIFT Package Insert

Hi Scott
of course this warning is ok for me but probably it is a rare event, and we should add something about the potential pain or dyspareunia in the postoperative course ?
sincerely
michel cosson
-----Message d'origine-----
De : Ciarrocca, Scott [ETHUS] [mailto:SCiarro2@ETHUS.JNJ.com]
Envoyé : jeudi 26 janvier 2006 14:23
À : Bernard Jacquetin (E-mail); Michel Cosson (E-mail)
Cc : Robinson, David [ETHUS]; Berthier, Ophelie [ETHFR]; Bonet, Giselle [ETHUS]
Objet : PROLIFT Package Insert

Warm Greetings Professors Jacquetin and Cosson -

It has been too long since we have spoken or corresponded! Hope you are both well and had excellent holidays with your families.

We have just recently completed a comprehensive review of our PROLIFT complaint / complication database for 2006. You will be pleased (as we were) to know that our complaint rate for the system is extremely low. Discussions with our US clinical investigators have led us to consider 1 additional item under ADVERSE REACTIONS. Specifically the proposed wording of this addition is as follows:

"Dissection for Prolift and any similar procedure has the potential to impair normal voiding for variable length of time."

Could you please offer your opinion on this addition plus any other additions to ADVERSE REACTIONS or WARNINGS / PRECAUTIONS which may be appropriate?

Scott Ciarrocca

ETH.MESH.00870466

Ethicon Expert Meeting
Meshes for Pelvic Floor Repair
Friday, June 2, 2006; Location: Oststr. 1, Norderstedt, Meeting Room "Forum"

Vaginal pain after implantation of meshes is rare, but feared, since there is not real treatment option (V. Lucente: prefer 20 recurrences or Erosions over 1 pain patient)

ETH.MESH.00870466

Biological response to surgical mesh (Prof. Klosterhalfen)
Huge surface area of meshes (e.g. more than 300 m of suture)
Even after 20 years the tissue is still reacting to the mesh.
Fibrosis is responsible for complications in mesh usage. ' Redacted
compared to PP
Foreign body reaction:

- Fibrinogen and Albumin bind to biomaterial, change and activate the immunologic syster
- active process, a "chronic wound", to be demonstrated by proliferating and dying cells
- combination of material and genetics.

Optimum pore size is material dependent (critical pores size; at least 1-2mm), scar formation a combination of pore size, surface area, polymer.
Large pores: fibrosis on the mesh fiber only
Small pores: interconnection between mesh pores due to fibroses leading to mesh shrinkage.

Shrinkage of 20% means reduction of mesh area to 64%

Tension of the mesh changes pore size → change in elasticity
Films or Foils cause more shrinkage than meshes
Meshes can cause Nerve damage due to mechanical irritation (mesh bears on nerve)
There is no inert material

Unmet clinical needs	**Priority (points)**
No shrinkage / no long-term contraction Fibrosis reduction Severe contraction → Dyspareunia → sexual function ↓ *Tension response ↓* = ↓ *Sexual pain?* *No folding of mesh* *No rigidity*	10
No vaginal distortion, normal vaginal wall, maintain sexual function, normal sexual function	8

ETH.MESH.01184119

2009 Surgeon Summit Breakout Session – February 7
Survey Results

PROLIFT™ Pelvic Floor Repair Systems

The improvements requested for PROLIFT are mostly around training; this is felt to be a big need. There is not sufficient education regarding peri-obterator anatomy and there is a failure of surgeons to understand the anterior apical passage. Also, depth of dissection needs to be emphasized more. It was suggested that training should be tiered, and stage gates should be implemented, in which surgeons demonstrate an understanding of training prior to moving onto cadaver labs. Other areas of

ETH.MESH.02289896

ETHICON
Women's Health & Urology

POP or PFTM?

- Post-op: Severe pain in LLQ, retention for 2 weeks and mesh exposure at 4 weeks
- Revision of exposure and DX LAPS at 6 weeks (adhesiolysis)
- Persistent pain, unable to have sex or stand for more than 1 hour due to pain, voids every 30-60 min
- Recurrent mesh exposure at 4 months

I have at least 4 pts with this problem sent to me. I feel that the pts start w/ mild POP and PFTM. The aggressive surgery flares the pre-existing myofascial pain. WE should therefore review with our doctors the difference between POP and the "pressure" of PFTM. POP does not cause pain!!! Look for symptoms >> degree POP

P1706 (June 2009)

Conclusion

Mesh shrinkage

- Is real !
- Occurs during the scarring and remodelling process
- May result in a unpredictable way in severe complications including dyspareunia, pain and recurrence
- May require mesh removal
- Must be taken into consideration during patient councelling before surgery

Is a challenge for the next years !

⇒ Need for a better understanding
⇒ Need for a better assessment
⇒ Need for a better material behaviour (and techniques)

ETH-80249

From: David Robinson
Sent: Friday, October 28, 2005 06:19 PM
To: Bonet, Giselle [ETHUS]
Subject: forgot

Dear Marty,
I know this will be my problem instead of yours soon but I need some advice. I am now aware of 4 cases of total Prolifts done in folks with normal preop voiding function (at least normal residuals and normal simple uroflows) who, then, post Prolift, can't void. Post op urodynamics show bladder atony rather than any obstruction. I have had two, Dennis Miller has at least one, and now Eric Webb called me with one today who is 5 weeks out. Some of these have resolved spontaneously but have taken as long as a year to do so.
Has this particular problem been reported? We are going to have to look at this because the cases seem to have no common thread or any difficulty with the surgery itself. But if this starts getting reported, it is going to scare the daylights out of docs.

ETH.MESH.04096233

-----Original Message-----
From: Chen, Meng [ETHUS]
Sent: Thursday, July 19, 2007 1:30 PM
To: Pelkey, Brian [ETHUS]; Yale, Mark [ETHUS]
Cc: Holloway, Carol [ETHUS]; Brennan, Carolyn [ETHUS]; Scavona, Joseph [ETHUS]
Subject: Prolift-post-op complication
Importance: High
Sensitivity: Confidential

Brian and Mark: Because a new case of ureter obstruction after Prolift just came in, and there were three others in my recollection, I would want to "cry wolf" once. I searched the Remetrex from March 06 to now. Out of 32 post-op complications, there are six ureter (the two channels bring urine to the bladder, not urethra) constriction or obstruction (including one bladder neck obstruction), about 20%. I am raising this issue to you for the following reasons:

1. Out of the 32 post-op complications, ureter obstruction should be considered the most serious. It could be rapid progressing to cause hydronephrosis and compromise renal function within a short period of time.
2. Ureter obstruction is not specifically mentioned as an adverse reaction in the Prolift IFU.
3. 20% of all post-op complication should be considered very significant, and my glance at all others, nothing else occupy such huge proportion.
4. From Dave's communications with the operating physicians, the doctors seemed not certain on how to diagnose and/or deal with the complication once confirmed.

5. It seems that because it is not listed in the IFU, there is no standardized or unified solutions, and Dave could not give specific advice. But the condition can be fast moving.

ETH.MESH.00133497 (Note: Voiding Dysfunction not added to IFU until 2009)

From: Robinson, David [ETHUS]
Sent: Mon, 21 Nov 2005 12:22:25 GMT
To: Selman, Renee [ETHUS] <RSelman@ETHUS.JNJ.com>; Hart, Dr. James [ETHUS] <JHart7@ETHUS.JNJ.com>; Mahar, Kevin [ETHUS] <KMahar@ETHUS.JNJ.com>; Staub, Linwood [ETHUS] <LStaub1@ETHUS.JNJ.com>; Bonet, Giselle [ETHUS] <GBonet3@ETHUS.JNJ.com>
CC: Weisberg, Martin [ETHUS] <MWeisbe1@ETHUS.JNJ.com>
Subject:

See attached summary of meeting at AAGL with Dennis Miller, Vince Lucente, Bob Rogers as consultants re: voiding probs post Prolift. As a consequence of this, Scott Ciarroca asked for wording to be added to the Adverse events section of IFU which I have suggested.
Dave

David Robinson, M.D., F.A.C.O.G.
Medical Director
ETHICON Women's Health and Urology

Discussion:
Any procedure which requires lateral dissection involving the pubocervical fascia (fascia endopelvina) or trigone puts the nerves of the bladder at risk for disruption. Seen by design in Ingleman-Sundberg operation which was done for refractory overactive bladder but isn't being performed any more since the nerves recovered within months of the procedure. The same process is being seen here but there is question as to whether the presence of the mesh in any way slows down the recovery. Other factors may further aggravate the voiding problem (general or epidural anesthesia, catheter use, anxiety). Recovery should occur spontaneously, though it might be months rather than weeks.

Conclusion:
This complication is not unique to Prolift but can occur with any procedure involving dissection described above. However, we should consider counseling our customers at the upcoming Prolift meeting so they will be able to counsel their patients appropriately and we need to check IFU for wording re: this problem. If need be, we should discuss whether to consider revising the IFU. Resolution should eventually occur spontaneously. Intermittant catheterization is an ideal management technique for this complication. Finally, we should consider performing animal studies (if an appropriate model can be found) to identify sites of nerve disruption and whether mesh retards recovery.

ETH.MESH.03923931 (Press Interview, Frankfort, June 9, 2005)

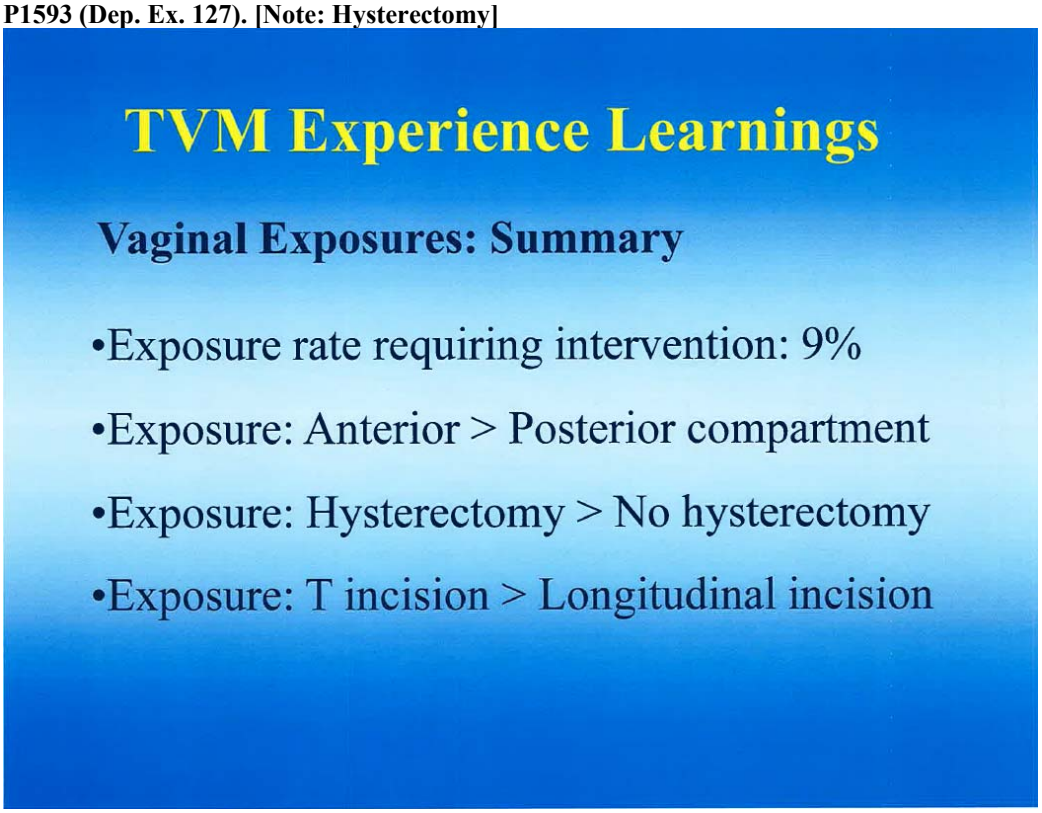
Comments

1. Mesh exposure is usually a minor complication. It can get cured most of the time by a simple excision of the part of the mesh that is apparent and a new vaginal closure.
Interestingly, the preliminary experience led to the identification of two key factors for the formation of an exposure:

- a concomitant hysterectomy:
- longitudinal incisions in the vagina.

Logically, the Group decided to change the type of the vaginal incisions and challenged the need for a systematic hysterectomy during prolapse surgery. This led to a dramatic decrease of the mesh exposure rate (<1%) when hysterectomy was not performed.
2. Shrinkage is due to an excessive scarring process. Even if most of the time it is asymptomatic, in a few cases it led to vaginal distortion impacting the sexual life. Thus, the procedure must be used cautiously in sexually active women.

P1593 (Dep. Ex. 127). [Note: Hysterectomy]



T-3321 (ETH.MESH.04082973) (Dep. of Meng Chen, MD, PhD)

Long term post-operative:

Persistent vaginal discharge (4.7%)
Vaginal bleeding (1.6%)
Dyspareunia (6.3%)
Sexual dysfunction
Recurrent prolapse (2.5%)
Mesh erosion (8.2%)
Obstructive voiding complications (11.0-18.3%)

Predictive Risk Factors for CV and Pulmonary Complications

- Age over 40
- Smoking history
- Obesity
- The presence of varicose veins

Other factors to consider

- Age
- Weight
- Parity
- Menopause status
- Estrogen therapy
- Previous surgeries
- Degree of pre-operative prolapse

c. Ethicon Did Not Perform Clinical Trials

ETH-00930

No clinical evaluations have been performed on the GYNECARE PROLIFT+M system. As PROLIFT+M is a Class II device (Product Code: FTL), demonstrating substantial equivalence to the predicate devices has been done with pre-clinical benchtop testing, and additional cadaver testing. This type of testing has been sufficient to demonstrate substantial equivalence for the identified predicates devices.

ETH.MESH.03915790

-----Original Message-----
From: Arnaud, Axel [ETHFR]
To: Azam, Usman [ETHUS]; Robinson, David [ETHUS]; Foltyn, Ted [ETHUS]
Sent: Mon Nov 13 11:41:23 2006
Subject: Pelvic Floor/Mesh Strategy

Oz/Dave/Ted

Some thoughts I could not pass during our call on friday:

1. Lightning
We should not forget the rationale behind this project. We set up a meeting with some experts, including I. Deprest and we asked them how we could improve the Prolift mesh. It came up that there are two issues with Prolift: erosion and shrinkage. Regarding erosions, whether a change in the mesh could result in any improvement is unknown as there is no certitude that the problem is mesh-related. It could as well be a surgical issue. The responsibility of the mesh seems to be more established regarding shrinkage and further to the expert's discussion, it was speculated that Ultrapro could be a solution for this problem, which is less common but can be more severe than erosion.

ETH.MESH.03915790 (continued)

I am a bit frightened to see that we are currently building a full business story on that, not having yet validated the proof of concept, neither from animal experiments nor from clinical use.
In my opinion, a logical way to proceed would be 1) to ask Deprest, for example, to compare Lightning and Gynemesh in animals and tell us if the theoretical assumption of less shrinkage is likely to be true 2) if this would be the case, we could then move on to clinicals and perform an observational study to confirm the benefits in humans 3) we could then discuss the need for a formal RCT to compare the two meshes and generate evidence that Lightning is a better choice than Gynemesh.
Alternatively, we could skip 1) and move directly to 2). If we ended up with results that would look better or at least equal to Gynemesh, we could certainly introduce the product on the market with a good chance of success (if reasonably priced) since the concept of light mesh is appealing on a surgical standpoint. If we are successful on the market, it is very unlikely that we will need to set up any RCT.
Finally, we could skip 1) and 2) and go directly for a comparative study. I do not believe this would be the best option, as it seems to me it would be expensive, long and risky.
To summarize, I support the idea of a single arm observational study.

P1143 (ETH.MESH.02923305)

From: Doherty, Anne [ETHGB]
Sent: Mon, 15 Aug 2005 09:55:55 GMT
To: Hunsicker, Kimberly [ETHUS] <KHunsick@ETHUS.JNJ.com>
Subject: FW: PROLIFT

FYI
-----Original Message-----
From: Linda Cardozo [mailto:lcardozo@compuserve.com]
Sent: 15 August 2005 10:53
To: ADohert1@ethgb.JNJ.com; anthony.smith@cmmc.nhs.uk; abdul.sultan@mayday.nhs.uk; ranee.thakar@mayday.nhs.com; mairecasement@hotmail.com; david.richmond@lwh-tr.nwest.nhs.uk; liz.adams@lwh-tr.nwest.nhs.uk; philip.toozs-hobson@bwhct.nhs.uk; chris.landon@leedsth.nhs.uk; tim@tsayer.co.uk; alfred.cutner@uclh.org; ian.ramsay@sgh.scot.nhs.uk; a@monga1.fsnet.co.uk; s_bjoornsson@msn.com
Cc: whitehead.whitehead@cmmc.nhs.uk; colette.davies@lwh-tr.nwest.nhs.uk; tina.cooper@nhht.co.uk.jnj.com; lindsey.dodds@leedsth.nhs.uk
Subject: RE: PROLIFT

Dear All

I have now had an opportunity to look at the complications associated with the TVM procedure. As I am not going to be able to attend a meeting in the afternoon of Tuesday 13th August in Montreal because of ICS commitments I thought I would just let you know that I find the safety profile quite worrying and hope that this will be discussed in some detail especially in view of the fact that we have no efficacy data to review. It is not that there were a lot of complications, its severity and type of complications and these were just the peri operative ones! I still have major concerns regarding the erosion rate and possible problems with dyspareunia and none of these have been addressed in the data which we have been given to date.

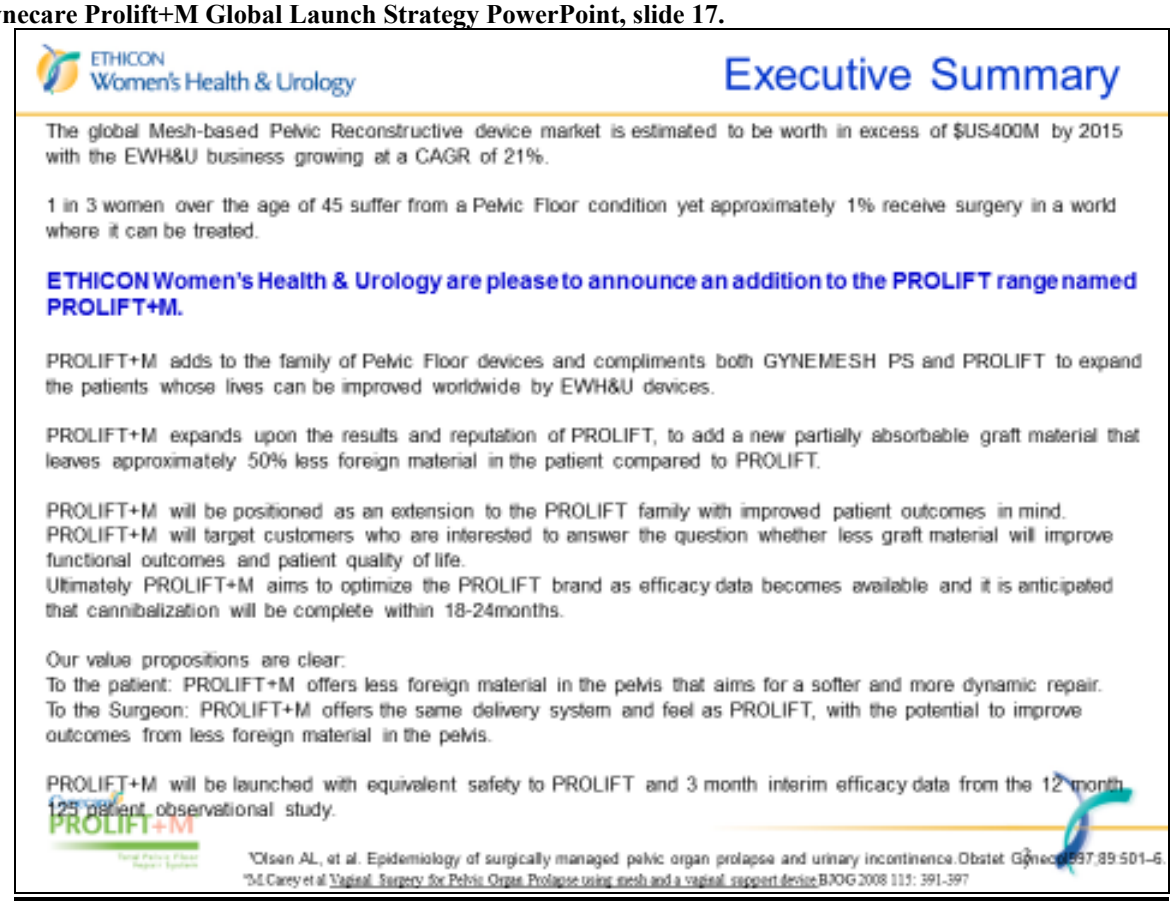
Unfortunately I am unable to attend the training sessions in Lille on either September 27th or October 25th but obviously I would wish to avail myself of a training opportunity if we are going to embark on a trial.

If the meeting does go ahead in Montreal please keep notes for me and let me know what your decision is as I would tend to be guided by the majority!

Kind regards

Linda

Gynecare Prolift+M Global Launch Strategy PowerPoint, slide 17.



ETHICON Women's Health & Urology

Executive Summary

The global Mesh-based Pelvic Reconstructive device market is estimated to be worth in excess of $US400M by 2015 with the EWH&U business growing at a CAGR of 21%.

1 in 3 women over the age of 45 suffer from a Pelvic Floor condition yet approximately 1% receive surgery in a world where it can be treated.

ETHICON Women's Health & Urology are please to announce an addition to the PROLIFT range named PROLIFT+M.

PROLIFT+M adds to the family of Pelvic Floor devices and compliments both GYNEMESH PS and PROLIFT to expand the patients whose lives can be improved worldwide by EWH&U devices.

PROLIFT+M expands upon the results and reputation of PROLIFT, to add a new partially absorbable graft material that leaves approximately 50% less foreign material in the patient compared to PROLIFT.

PROLIFT+M will be positioned as an extension to the PROLIFT family with improved patient outcomes in mind.
PROLIFT+M will target customers who are interested to answer the question whether less graft material will improve functional outcomes and patient quality of life.
Ultimately PROLIFT+M aims to optimize the PROLIFT brand as efficacy data becomes available and it is anticipated that cannibalization will be complete within 18-24months.

Our value propositions are clear:
To the patient: PROLIFT+M offers less foreign material in the pelvis that aims for a softer and more dynamic repair.
To the Surgeon: PROLIFT+M offers the same delivery system and feel as PROLIFT, with the potential to improve outcomes from less foreign material in the pelvis.

PROLIFT+M will be launched with equivalent safety to PROLIFT and 3 month interim efficacy data from the 12 month 125 patient observational study.

PROLIFT+M

[1]Olsen AL, et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997;89:501–6.
[2]M Carey et al Vaginal Surgery for Pelvic Organ Prolapse using mesh and a vaginal support device BJOG 2008 115: 391-397

ETH.MESH.00075065

-----Message d'origine-----
De : Robinson, David [ETHUS]
Envoyé : vendredi 13 juillet 2007 20:27
À : Berthier, Ophelie [ETHFR]; Lisa, Bryan [ETHUS]; Subramanian, Dhinagar [ETHGB]; Shen, Jessica X. [ETHUS]; Guidry, Cyrus [ETHUS]; Gauld, Judith [ETHGB]
Cc : Zaddem, Vincenza [ETHUS]; Meek, Jonathan [ETHUS]
Objet : RE: Lightning Launch Planning Stage Gate Preparation

Dear Ophelie

I have met with Judi Gauld, Jessica Shen and Bob Roda this morning. Part of the discussion centered on your question regarding what will be available at the time of the launch of Lightening. Your email quoted the May/June time frame as the launch date. Is this the date of the planned European NTM?
After presenting options to the Board, the Board made the decision to launch with only soft or no data depending on what time frame you consider. The planned observational study will collect 3 month data on all 60 patients which we would submit to IUGA for consideration in 3/08. Obviously, if accepted and then once presented and copy reviewed, it can be used internally and externally. Once submitted to IUGA, we believe it can be used in sales pieces by referencing "data on file" but nothing will be available to leave with doctors.
As I understand it, the "pre-launch" activities will involve limited KOL use as early as 11/07 if product is available. That would be done with previous UltraPro hernia data. Additionally, a further "limited launch" would occur following the US NTM date TBD, again with previous UltraPro hernia data.
I hope this helps clarify the picture.
Dave

P.1659 (Characteristics of Synthetic Materials Used in Prolapse . . . Surgery)

It is a challenging task to try to define the ideal material for pelvic floor surgery. Indeed, the scientific knowledge about the use of meshes in surgery is still in its infancy, at least for pelvic floor applications. There are far more products available on the market than randomized comparative trials which could help making a clear distinction among them.

In the absence of strong clinical evidence, one have to rely on various sources to try to help the surgeons to make an appropriate choice when considering the use of a synthetic material. These are essentially: basic knowledge from the science of textiles, clinical and fundamental research from hernia surgery and results of the more recent clinical experience in pelvic floor reconstruction.

Thus, all the recommendations that might be given in this presentation must be viewed with respect to these difficulties of finding hard data. They should certainly be reconsidered on a regular basis as long as more evidence is made available by the searchers.

ETH.MESH.03916207

From: Berthier, Ophelie [ETHFR] <OBERTHIE@jnjfr.jnj.com>
Sent: Thu, 12 Jul 2007 11:15:04 GMT
To: Robinson, David [ETHUS] <DRobin11@ETHUS.JNJ.com>; Lisa, Bryan [ETHUS] <BLisa@ETHUS.JNJ.com>; Subramanian, Dhinagar [ETHGB] <DSubrama@ethgb.JNJ.com>; Shen, Jessica X. [ETHUS] <JShen@ETHUS.JNJ.com>; Guidry, Cyrus [ETHUS] <CGUIDRY2@ETHUS.JNJ.com>; Gauld, Judith [ETHGB] <JGauld@ethgb.JNJ.com>; Arnaud, Axel [ETHFR] <AARNAUD@jnjfr.jnj.com>
CC: Zaddem, Vincenza [ETHUS] <VZaddem@ETHUS.JNJ.com>; Meek, Jonathan [ETHUS] <JMeek1@ETHUS.JNJ.com>; Burns, Janice [ETHGB] <JBURNS5@ethgb.jnj.com>; St. Hilaire, Price [ETHUS] <PSTHILAI@ETHUS.JNJ.com>
Subject: RE: Lightning Launch Planning Stage Gate Preparation

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Dave,
Thanks for responding quickly. Does that mean that if the abstract is refused, we will have no data to communicate to the salesteams?

In addition, I am still not clear what exactly we will be able to provide salesforce for their training and external customer once we launch from the Lightning clinical study. Because even if we don't have massive data to show customers, being able to provide at least some mesh exposure or erosion rate will be something we will need, nb of patients, immediate post op complications and per op complications will be useful to launch properly Prolift+M. Do you who could help there?

Bryan,
Can't we use data with the quote "internal file data" to issue a powerpoint slide or two with few datas to comunicate to our salesforce and customers?

Thanks a lot for your help and support,

Ophélie

ADDITIONAL DISCLOSURES

I may be asked to review additional materials and/or documentation as the case progresses and, in that event, I reserve the right to supplement this report. My current hourly fee is $650/hour, not including testimony.

During the previous four years, I have testified as an expert witness at deposition or trial in the following cases:

In re: C.R. Bard, Inc. Pelvic Repair Sys. Prods. Liab. Litig., MDL No. 2187 (S.D. W.Va.)
Nava v. Boston Scientific Corp., et al., Civ. Action No. 2:13-cv-14455 (S.D. W.Va.)
In re: Boston Scientific Corp., MDL No. 2326 (S.D. W. Va.)
Callen v. C.R. Bard, Inc., Civ. Action No. 2:14-CV-14375 (S.D. W. Va.)
Harrison v. C.R. Bard, Inc., Civ. Action No. 2:12-CV-06602 (S.D. W. Va.)
Huber v. C.R. Bard, Inc., Civ. Action No. 2:13-CV-02424 (S.D. W. Va.)
Jay v. C.R. Bard, Inc., Civ. Action No. 2:13-CV-08536 (S.D. W. Va.)
Rueda v. C.R. Bard, Inc., Civ. Action No. 2:13-CV-02175 (S.D. W. Va.)
Smitty v. C.R. Bard, Inc., Civ. Action No. 2:13-cv-33750 (S.D. W. Va.)

This 1st day of February, 2016.

Bob L Shull MD.

Bob Shull MD